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Essays on the Internal Secretions

1920

Comprising the Winning Contributions, *with* Some Others, to the First "Harrower Prize Essay Contest."

Edited by

HENRY R. HARROWER, M. D., F. R. S. M. (Lond.)

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Glendale, California

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ESSAYS ON THE INTERNAL SECRETIONS—1920

I

INTRODUCTION

FOR MANY YEARS the writer has been especially interested in developing information pertaining to the internal secretions, and in many ways has attempted to further the interest of the profession in the subject. The establishment of the Association for the Study of the Internal Secretions in 1916 was the result of his invitations to numerous correspondents to band themselves together in order to exchange views and make possible a bulletin reflecting the progress in this field.

While The Harrower Laboratory is a commercial institution, concerned with the production and sale of certain endocrine remedies, its work is by no means limited to this. In fact, the manufacture of these formulas was undertaken in order that funds would be available for research and other work necessary to materialize the writer's ideals.

Among several efforts to broaden the interest and information on the practical aspects of the internal secretions is a Prize Essay Contest which was announced early in 1920. Five hundred dollars was offered to members of the medical profession (and medical students) for a series of essays on the internal secretions. This money was divided into five prizes

as follows: First, $250.00; second, $100.00; third, $75.00; fourth, $50.00, and fifth, $25.00. Quite a number of competing essays were received from several different countries, and the best of them will be found in this volume.

Naturally, it was not the intent of this contest to find a means of disposing of $500.00 amongst five essayists, but rather to gather together a number of efforts from different sources in order that they might be made available for the clientele of The Harrower Laboratory and such physicians as might care to avail themselves of this opportunity to get some additional suggestions in this special line of study.

It must be understood that each subject is considered from an entirely different viewpoint, because each essay is prepared by a different person, whose interests, medical environment and literary facilities differ very materially. In some instances there may be a slight redundancy because it happens that several writers may be discussing the same subject and necessarily must repeat certain fundamentals that would be found in another paper on the same subject. This repetition, to my mind, is an advantage, because in this way the fundamentals are reiterated and the impression that they may make becomes the more lasting.

It has been decided to extend another invitation to physicians, both here and abroad, to contribute essays in another similar contest for which the same amount —$500.00—divided in the same manner, will be offered in 1921. The rules of this contest will be identical with this year and printed instructions and an individual contest number will be sent to any interested physician on request prior to June 30, 1921. It is planned to close the contest at the end of September and to announce the prize winners before the end of the year.

It may be that some reader to whose attention this collection of essays may come has some criticism or comment to make, and it is requested that if this occurs copies of the letters directed to the essayists be sent to the undersigned in order that he may benefit from such correspondence.

In closing I desire to express appreciation to those who have interested themselves in this contest, and especially to Dr. Edwin B. Tuteur, of Chicago, who very kindly assisted me in determining the disposition of the prize money.

HENRY R. HARROWER.

The Harrower Laboratory,
Glendale, California,
February, Nineteen Twenty-one.

II

THE BASIC PHYSIOLOGIC REGULATORS

By W. M. Lowe, M.D., Lometa, Tex.

The physiologic functions essential to perfect health, are:

(1) Normal circulation.
(2) Normal respiration.
(3) Normal temperature.
(4) Normal assimilation.
(5) Normal sexuality.

These essential functions are dependent upon:

(1) Perfect action of the heart.
(2) Perfect action of the lungs.
(3) Perfect action of the digestive organs.
(4) Perfect enervation. These taken together give:
(5) Perfect sexuality. Imperfect sexuality during the sexual life of an individual is a strong symptom of abnormal health.

It is obvious that in order to have perfect action of these organs they must be free of all disease *per se*—in perfect health. Also, it is evident that the actions of these organs are often disturbed by an acute infection of some other organ or portion of the body. Thus, an erysipelas of the hand will temporarily disarrange all those organs.

But every physician of experience has found many people in ill health when the most painstaking examination would fail to reveal any diseased condition of either the heart, the lungs, the digestive organs or the

nervous systems; also, those people might be free from an infection of any organ or portion of the body. This class of patients usually consists of the chronics who have a long train of symptoms that point to imperfect action of one or more of the vital organs—imperfect circulation, difficult respiration, subnormal temperature, high or low blood-pressure, malassimilation, defective elimination, nervous prostration, sexual incompetency and such like.

The question arises: Why this imperfect actioning or malfunctioning of the vital organs in the absence of any disease *per se*, and what is the best known treatment? The answer to this very important query brings us to the consideration of the subject indicated by the title of this paper: "The Basic Physiologic Regulators," or the ductless glands and their secretions, usually known as the internal secretions or hormones.

I am free to admit that I had been a student of medicine for twenty years, and an active practitioner fifteen, before I had anything like a clear conception of the physiologic role of the endocrine glands, or that dysfunction on the part of one or more of them would unbalance the physiologic poise of the body and thereby cause a state of general ill health.

It has been repeatedly stated that the human body is a machine. For the sake of comparison, we will admit the truth of this rather materialistic expression and compare the physiologic functions of the endocrine glands to the regulator that controls the actions of a watch. The minute mechanism of a watch may be perfect, not a break nor flaw in any of its wheels, pinions, levers or springs—in normal "health." Yet, unless that delicate mechanism known as the regulator is accurately adjusted the watch will not keep perfect time—it will run too slow or too fast. So with the human body. Every vital organ may be in perfect health *per se*, without pathologic lesions, yet, unless the

basic physiologic regulators, the internal secretions, are in perfect adjustment—in what might be called a physio-chemical equilibrium—those organs will not function in harmony. Some or all of them either will run too slow or too fast with a resultant state of ill health.

The most important of the endocrine glands may be roughly classed physiologically, thus:

(1) *The Thyroid;* metabolism, growth, antitoxic.
(2) *The Adrenals;* blood-pressure, arterial tension, muscular tone.
(3) *The Pituitary;* heart, unstriped muscles, renal secretion.
(4) *The Gonads;* sexuality, reproduction.

The secretions they manufacture are called "internal" because they go directly into the circulation without first being conveyed into other glands or organs or undergoing any change. Hence, they are internal with reference to the blood current.

Speaking in a general way, the adrenals and pituitary control the action of the heart. Either a hyper- or hypo-function of these glands will disturb the stability of its action. Either it will lose its normal power of contraction, become enfeebled—blood-pressure low, circulation retarded, extremities cold, more or less edema of the lungs and viscera—hence, difficult respiration and imperfect digestion; or else the heart will contract with too much force—the blood pressure is high, skin flushed, high nervous tension, headache more or less constant, apoplexy threatening. Such are the chief symptoms of adrenal dysfunction.

To the consideration of these two, let us add another, the thyroid. This gland, taken in connection during early life with the thymus, influences the growth and development both physical and mental of the child. During adult life it continues to influence metabolism; also, it has remarkable antitoxic action. Therefore, the grave pathological effect of any disturbance of its

action is apparent: gastric, intestinal and renal derangement, giving indigestion, malnutrition and faulty renal elimination—all of which lowers the vitality and bodily power of resistance to infection, which usually follows.

Now, to complete the picture of endocrine disorder, let us consider the gonads. The gonads either make or mar reproductive capacity and the sexual life of the individual. On them depends not only the propagation of humanity but that greatest of all the propensities, sexual instinct, upon which rests that greatest, strongest and most ennobling of all the emotions—love—that binds together families, communities and races, and is the foundation of modern society and civilization.

Anatomically, the gonads are not ductless glands; but, in addition to their reproductive usefulness, it is now an unquestioned fact that they manufacture an internal secretion, which is correlated with the hormones of the true ductless glands in maintaining the physio-chemical balance of the body.

When we think of sexual disorders it is but natural that we think of the sexual organs. However, in a majority of such cases, the primary, underlying cause really is with the other ductless glands. Indeed this seems to be true of practically all cases except tuberculosis or specific infection.

Too often we have seen the healthy, robust, energetic and kind husband and father become a sickly, miserable, cruel and worthless man. And oftener, we have seen the young, healthy, tenderly-loving wife and mother develop into a sickly woman, displeased and disgusted with husband, home, family and life in general. Such conditions are the instigating cause of many separations and divorces.

It would be a waste of time and effort to give in detail all the symptoms of such cases—loss of appetite; indigestion; nausea; sexual frigidity; irregular, diffi-

cult and painful menstruation, with the accompanying back and headache; hysteria; melancholia; neurasthenia are symptoms with which we all are familiar.

From time immemorial we physicians have been treating those patients by giving sedative, tonic, and digestive drugs, also operations, electricity, baths, massage and suggestion with little or no success at all.

Now, it is in the treatment of just such cases that I have had the most successful results with the glandular extracts. I dare say you could hardly find a physician who is not familiar with the action of adrenalin or who has not witnessed the immediate and powerful specific effect of pituitrin on the uterus at the obstetric bed. Yet, there are some doctors who doubt the efficacy of the other organic extracts. They also doubt the efficacy of those two in so far as being remedial in the treatment of disease. However, the number of the doubters is rapidly declining. Those who remain are of two classes: Those who have never had any experience with organotherapy, who have not given the matter any deep thought; and those who have used only the monoglandular extracts, losing sight of the fact that the endocrine glands are so closely interrelated that a monoglandular dysfunction is, perhaps, a physiological impossibility.

I report in detail the following case as being typical of endocrine dysfunction, and evidence of the results of pluriglandular treatment. No doubt the condition of this poor woman can be paralleled many times by any physician of a few years' experience, especially those giving attention to chronic ills:

Mrs. R. F. W., age 36, mother of three children, youngest three years. No abortions. Family history good. Personal history good until beginning of present illness.

Present illness began in November, 1918, closely following influenza. In so far as the special symptoms of influenza were concerned she soon recovered, but soon noticed that her digestion was not normal. She would

cramp after meals; "belched" a great deal, and was constipated at times; at other times, the bowels were too loose. She suffered from many headaches, and soon became very nervous with insomnia to aggravate matters. There was a marked bodily weakness, and the patient tired very easily.

I examined this woman first about a year ago, at which time I found as follows:

Much abdominal distention; inability to digest food; malnutrition very evident; menstruation irregular, scanty and difficult; complete sexual frigidity. (Discussing this matter with her, I learned that her sexuality had been rather unusually strong, but that shortly after recovering from the influenza it was for a short while more pronounced than ever. "It seemed that I could not keep that out of my mind," was her statement.) Pelvic pains and cramping frequent; uterus and ovaries tender; slight leucorrhea; blood-pressure low; pulse fast and feeble; subnormal temperature; feet more or less edematous.

Believing this to be a case of beginning pellagra, I began treatment by giving hypodermics of sodium cacodylate. After thirty days, there being no improvement apparent, I discontinued the arsenic and began a stock pluriglandular formula containing adrenal, thyroid and spermin. After three weeks her general condition was beginning to improve. By the end of the second month, on this treatment, her temperature and blood-pressure were normal. The gastric and intestinal symptoms had subsided and she was being well-nourished. At six months she had regained her normal health.

Another case; Mrs. J. M. H. She was in the second month of her third pregnancy; was vomiting almost incessantly, and, of course, was very nervous. I began treatment by giving Ext. Corpora Lutea subcutaneously, and such antiemetic drugs as are usually given in those cases. After two weeks there was no improvement. I then discontinued everything and began the same pluriglandular treatment, with the result that at the end of the third week the vomiting had stopped and did not return during the pregnancy. This shows that hers was, also, a pluriglandular disturbance.

AN EXPERIENCE WITH A DEFECTIVE BOY

The most glowing success I have had—the one that gave me the biggest boost and brought the most joy to several people—with hormone treatment was in a case of "defective" development, or hypoplasia, as it is sometimes called, in a boy nine years old.

Not only was dwarfism very pronounced in this boy, but he was very "backward" mentally. He could only articulate a very few words; and had not even learned his letters. Eight months ago I put him on another stock prescription, this time containing thyroid, thymus and anterior lobe of the pituitary gland. I did not make any very bright promises as to results, because of a previous failure with thyroid, but had the parents' promise to keep up the treatment, interrupted during every fifth week, for at least twelve months. There was no apparent improvement during the first four months; but, two weeks ago the boy was brought to my office—the only time since the beginning of the treatment. "I have brought Albert for you to see how much better he is," the mother enthusiastically exclaimed. Well, that boy had grown two inches; could talk fairly well and his facial expression was entirely changed and was much brighter than before.

Now here is a case that would have, undoubtedly, been a wasted life, a physical and mental dwarf, a hopeless idiot, a burden to his family and society. But I am hopeful that by continuing treatment indefinitely he will develop into a fairly useful citizen. And, let me say, that not all the doubting doctors will ever be able to make this mother believe that the improvement in her boy is only a case of "coincidence."

Yes, organotherapy has come, and it has come to stay. Only a very few years ago the subject was seldom mentioned in the medical press. Now you can hardly pick up a medical journal without finding an

article dealing with some phase of hormone treatment. Only a few days ago I had a patient examined by a noted surgeon. "She needs glandular feeding, doctor," was his first suggestion. On being assured that I had had her on that kind of treatment for two months, he said: "Push the hormones long enough and you will get results; the ductless glands are undoubtedly at the bottom of all her trouble."

I predict that the next few years will bring wonderful advances along this line. And in the meantime we, as thoughtful and conscientious physicians, should give our patients the best we have, the treatment that will cure, or, at least, benefit them the most. Our own best interests and our sense of duty well done both demand it.

My experience during the past few years in the general practice of medicine, giving special attention to chronic cases, together with extended reading through the current medical literature, and discussing the matter with many of my medical friends, convinces me that in the treatment of many cases, not a few of them hitherto classed as incurable, we get the best results with the glandular extracts.

I will conclude with the following syllogism:

I.

1. The endocrines produce secretions which act as physiologic regulators in control of the vital and reproductive organs.

2. But, from causes, at times unascertainable, one or more may fail to functionate properly.

3. Therefore, the physiochemic balance of the body is disturbed, which, in turn, disturbs the action of the vital organs, resulting in bad health.

II.

1. Glandular extracts obtained from the lower animals, not only supply the chemical deficiency, but stim-

ulate to action those corresponding organs in the human body.

2. When the endocrine deficiency is restored the vital and reproductive organs functionate normally again and the health of the individual is restored.

3. Therefore, organotherapy is rational and gives results.

III.

1. The ductless glands are so closely interrelated that dysfunction of one shortly disarranges the entire endocrine system.

2. Monoglandular extracts stimulate to action only one gland.

3. Therefore, plurglandular formulas should be used; they give the best results in the greatest number of cases.

III

SOME CLINICAL ASPECTS OF ENDOCRINOLOGY

By F. J. Farnell, M.D., F.A.C.P., Providence, R. I.*

"One thinks metaphysically; but one lives and acts physically." Descartes.

Should one be called upon to consider the most important factors necessary for complete harmony in one's self, the first thought would be, undoubtedly, one's own self. And yet, is that all that is necessary? "Know thyself" has long been recognized; but even then, without an harmonious environment, proper mental and physical adjustment oftentimes cannot take place. Sherrington once said, "environment drives the brain and the brain drives the body."

There is little doubt that exogenous factors play an important part in the response or *rapport* of the various physiological functions, which, when linked with poorly developed instinctive demands, unstable emotional activities or variations in the personality balance, causes a tendency towards a corresponding reaction affecting the tonus system which brings about a variation in the cardiovascular response, producing biochemical changes and metabolic disturbances with variations in the endocrine output.

In the discussion of this subject the writer will attempt to present a few aspects of its clinical significance, emphasizing those facts which indicate a quali-

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* *The writer of this essay received the third prize of $75.00.*

tative disorder. For the syndrome or complex types of a quantitative nature reference should be made to the works of Biedl,[1] Schaefer,[2] v. Frankl-Hochwart[3] and Falta.[4] The clinical picture in those quantitative endocrine disturbances will give one the well-recognized giant, the dwarf, the case of infantilism, Addison's disease, and so forth. That is, these quantitative types might be placed in the same group of disorders as any actually destroyed tissue or function, that of an organic or structural inferiority,[5] a lack of development (aplasia) or a cessation of function at a time comparatively earlier than the remainder of the body tissue. In those endocrine disorders, however, of the qualitative type the syndromes or symptom-complexes will be less marked in direct relation to any endocrine gland or group of glands and more marked in relation to the vessel tone and its effect upon the whole system.

It seems, therefore, quite essential to divide the body into such components as are involved in the so-called symptom-complex mechanisms. The author's theoretical and working divisions are the mucocutaneous, the cardiovascular, the internal secretory system, the autonomic (vegetative) nervous system, the cerebrospinal system; and the three important interrelating factors—personality, emotion and environment.

THE MUCOCUTANEOUS SYSTEM

If one could estimate theoretically the area of the skin it would equal, approximately, three by five feet. In addition, there should be considered the length and breadth of the gastrointestinal tract from the mucocutaneous junction at the mouth to the mucocutaneous junction at the anal opening.

Histologically the skin and mucous membrane might be divided theoretically into three parts, the glandular, the vascular and the neuromuscular. In the skin are the sebaceous and sudoriparous or sweat glands, the

cutaneous blood vessels and the dermal system of involuntary muscles (Gaskell[6]). Correspondingly, in the gastrointestinal tract are the secretory glands, the extensive vascular supply and the unstriped or smooth muscle extending from the middle third of the esophagus to the internal sphincter of the rectum. Each part of this mucocutaneous system is under neurogenic control either through the sympathetic, the autonomic or the cerebrospinal nerves, and these govern, undoubtedly, its biochemical and metabolic processes. Langley,[7] Schoff[8] and Sherrington,[9] have shown quite clearly the neurogenic control of the sweat glands, the erection of hairs, the phenomenon of "goose flesh," in the skin; and the hypersecretory activity of the intestinal glands, as well as the peristaltic rhythm of the component parts of the alimentary canal.

ENDOCRINE MANIFESTATIONS IN THE SKIN

If one should consider the approach towards the development of a diseased or disordered endocrine gland, is it not of primary importance to determine the activity of the sweat glands, the condition of the skin, the growth of hair, and such facts concerning the mucous membranes as can be seen? So characteristic are the signs manifest in the skin and mucous membrane accessories that the actual gland affected, either in its hyper- or hypoactivity, will depend upon the hyperidrosis, the dryness or smoothness of the skin, the lack of hair or its anatomical distribution, etc.

How often one will hastily diagnose a case as hyperthyroid or hypopituitary upon the excessive sweating in the former and the unusual hair distribution in the latter, and yet, oftentimes neither will react to the presumably indicated therapeutic measures. It is because of this tendency to enter the sphere of true quantitative disorders immediately that urges the writer to delay and emphasize these prequantitative types. For

example, a young man of 36 years, complains of loss of weight, excessive sweating, palpitation, and extreme nervousness. He has been recognized as a possible hyperthyroid case without obvious enlargement of the thyroid. Because of a tendency towards vomiting and periodic diarrhea he was thought to have had an ulcer of the stomach. In this case, without going further into detail, the important symptoms, such as excessive sweating, vomiting, periodic diarrhea, were looked upon as vasomotor in type. The loss of weight might be expected and the palpitation with arrythmia was undoubtedly neurogenic in origin. The Goetsch reaction[10] was distinctly negative.

On the other hand, a man of 38 years, weight 170 pounds, complains of sleepiness, fatigue, and is generally "slowed down," both in thought and action. His skin was sweaty and oily; his hair-distribution normal but "thinned out;" his pulse was irregular and the tension low, and he complained of nocturnal tachycardia. He also stated that his sexual desires (mental) had lessened, although he could be readily aroused. This picture is not unlike the Rénon and Delille syndrome,[11] indicating pituitary insufficiency, and yet the Goetsch test exaggerated all symptoms and made the patient most uncomfortable. Then, too, liquor hypophysis, unless given in very small doses, also exaggerated the complaints. Might not these symptoms also be of the vasomotor type? It is doubtful that the case was one of hyperthyroidism.

It is not uncommon, in taking the anamnesis of these patients, to be told that for a long time, or ever since the age of 13 or 14 years, they have been "nervous" and suffered more or less from so-called "nervous attacks," such as cold hands and sweating, or biliousness and constipation, or frequency of urination, even to the extreme of bed-wetting, headaches, and so forth. Then, in later life, an acute infectious disease, or an abdomi-

nal operation, changes the entire aspect of the case with a more definite settling of the picture. Some few cases are reported and seen where an actual tissue change has taken place in some one or more of the endocrine glands with a quantitative disorder. For example, a man of 59 years states that at the age of 32 he was infected with syphilis and treated with mercury for three years, and potassium iodide for seven years. Up to the age of forty his average weight was 150 pounds, and he was considered quite well. At that age he developed an acute illness, characterized by severe headaches, dizziness, and blurring of vision. He had pains all over his body, lost weight and flesh rapidly. He had some temperature and a diarrhea. He was in bed ten weeks. When he gained his feet again he noticed a decided change in his facies and the color of his skin. During the next year his hair dropped from his armpits and there was a gradual subsidence of secondary sex characters with loss of sexual activity, both sympathetic and cordial. He began to gain, and his weight increased up to 200 pounds. During the last five years he has taken all the various glandular products, alone and in combination, without any manifest change. His skin was rough, he complained of the cold, the skin of his hands and feet was thick and cracked, he never sweat. His hair was thin—he had little to shave upon his face—and he complained of muscular aches and pains. Last fall he was seen by the examiner. The Goetsch test was negative. Liq. Hypophysis (pituitrin) over a period of time seemed to have no actual effect. However, about eight months ago, he was given a 1/8 grain pilocarpine hydrochloride to test out his responsiveness through his sympathetic system. He sweat. The next week he felt much warmer, the coldness left his hands and feet; his bowels, which had always been constipated, moved freely. A change had undoubtedly taken place and it was followed by injec-

tions of the posterior pituitary solution. Within a few weeks his skin became soft and moist, with some sweating. His pains and aches left him; he said, "I feel looser." He lost weight, and much of his accessory fat deposits disappeared. Not only could he mentally call forth an erection, but he often had spontaneous erections. Might not the sympathetic stimulation have aroused some glandular activity, which is kept active by the injections? Or are these changes in the skin and vessel-activity only related to the vegetative system?

A case of postoperative disorder, with the "settling" of symptoms, was seen in a woman of 38 years, who was always "nervous," with indigestion, headaches, fatigue, and lack of ambition. Nothing seemed to give her relief. In October, 1919, she had a partial hysterectomy for a fibroid without the removal of the ovaries. For three months she improved physically, and then seemed to "slump," not with indigestion, headaches and "nervousness," but with a predominance of vasomotor disturbances related to her gastrointestinal tract. She developed angioneurotic edema of the mucous membrane of the mouth and anal cutaneous junction. Her mouth became filled with "canker," small patches of erosion of the membrane. Her tongue became very red, cracked and swollen. Her color was changed, and became of a "muddy" appearance, with attacks of areal blushing. Her skin was dry, her hair fell out, and her face and hands would "puff" or swell. Are not these predominating symptoms vasomotor in type? Is it a case of thyroid insufficiency (Laignel-Lavastine[12]), which was at a standstill for years, and which broke down following the operation? Could it have been a mixed "Basedowianism" disorder, as described by Sainton?[13] The Goetsch test was negative. The history of nervousness for years would point towards what has been termed a "vagotonic" disposition.

The operation broke down this "conditioned" system and signs of vegetative disharmony came forth with vasomotor inactivity in the foreground. An adjustment of her vessel-tone caused the immediate disappearance of the edema, "cankers," and swollen tongue. It is not possible that in the past such a disturbance would have been looked upon as a "reflex neurosis"—McGillicuddy,[14] Hilton[15]—and that little attention was paid to the developmental personality and vagotonic disposition?

THE CARDIOVASCULAR MECHANISM

The second system to be considered is the cardiovascular system, which is composed of the heart, a special type of smooth muscle tissue, and the enormous extent of blood vessels from the larger arteries to the small capillary tubes and lymph channels. The blood-vessels contain in their inner coat the smooth striated muscle tissue with its vasomotor nerve control. In the majority of quantitative glandular disorders there is a disturbance in the cardiovascular mechanism, either an arrhythmia, a hyper- or hypotension, brady- or tachycardia. These symptoms occur of themselves, as was noted in the physical examinations of the recruits for the army, and many were accepted as soldiers, who later developed actual neuroses, under the strain and stress of army life. Oftentimes this stress upon the "conditioned" cardiovascular system brought forth symptoms highly suggestive of a thyroid or an adrenal membrane, the vasomotor disorders in their peripheral blood-vessels appeared to be most important. In the cardiovascular system, *per se,* there are such symptoms as swooning, fainting, epileptoid seizures, convulsions, —pseudo-myocarditis, pseudo-angina pectoris. Laignel-Lavastine has said that endocrine syndromes may depend not only upon a lesion of a corresponding gland or its regulating nervous mechanism, but indeed upon

an upset of one or the other brought about by an infectious or toxic origin. So often this is manifest with the cardiovascular system, evincing the symptom-complex, and yet to direct one's energies towards that alone, and not seek for other disturbances, undoubtedly gives cause for the feeling that future permanent heart or blood-vessel disease may be the outcome of this indicator. The frequent attacks of cardiovascular instability, of neurogenic origin, may be the primary factors at play in the future, determining an arteriosclerosis of what we now call "idiopathic" origin. It also may be possible that the disturbance termed latent myocarditis is a smooth muscle neurosis, indicating a future pathology of the myocardium. Such conditions as intermittent claudication, the acute vasomotor paralysis described by Halley,[16] and Nothnägel,[17] as well as Raynaud's disease, may have as their fundamental disturbance a primary vascular neurosis. These toxic factors may produce transitory upsets in the nervous mechanism or glandular activity, resulting in distinct changes in the biochemistry of the blood and in the tissue metabolism. For instance: A young woman of 24 years, three weeks before her confinement, complained of frequent lapses of consciousness. She went her full time, however, and gave birth to an apparently normal child. The child died in convulsions on the eighth day. During these eight days, and for several weeks following, the mother had frequent attacks of loss of consciousness, "rolling of the eyes," and other epileptoid attacks. Approximately two months after her confinement she presented a systolic blow at the apex of the heart, a rapid arrhythmic pulse, peripheral vasomotor instability. She complained of headache, wept a great deal, had "shivering fits," hot flashes and sweats. Her blood examination showed the blood sugar 95 mg., urea nitrogen 18 mg., and kreatinin .4 mg. This disturbance in metabolism in conjunction with prepartum and post-

partum attacks led the examiner to increase the metabolic activity, with the result that within two weeks the attacks disappeared, and a second blood examination showed her blood sugar to be 125 mg., urea 16 mg., and kreatinin .28 mg. Was the primary condition an unstable thyroid brought into activity by pregnancy, or was it the toxico-biochemical changes affecting the nervous mechanism of the cardiovascular system?

A somewhat similar reaction was seen in a woman of 27 years, who gave birth to a child five months ago, and who, since then, has been unable to cope with her household duties. She has grown stout and complains of being weak and tired, with attacks of sweating, with cold hands and feet. Her systolic blood pressure was 90 mm., with a rapid, irregular pulse. There was a double systolic blow over the heart. In her history we find that she has always been anemic and nervous. She had an attack of "nervousness" five years ago, with palpitation of the heart, frequent nosebleed, and erythromalgia. After her marriage she gained in weight. Her urine examination was negative. The blood examination showed a blood sugar of 140 mg., a urea of 16 mg., non-protein nitrogen of 37 mg., and kreatinin of .18 mg. In this case all her complaints developed following her pregnancy, and are related to the cardiovascular system in an individual whose vascular system has been "conditioned" undoubtedly. Is this conditioning primarily an organic inferiority or a disturbance in the neurogenic mechanism with disturbances in metabolism?

THE ENDOCRINE GLANDS

The third system to be considered is the chain of endocrine glands. Histologically they are composed of secretory cells, supportive tissues and an extensive blood supply, which is under both the autonomic and sympathetic control. When there is an actual disturb-

ance in histological tissue, with a cessation or loss of function, the clinical picture is quite distinct. It will vary with the gland or number of glands involved and always be of the quantitative type. One may merely recall the cretin, the acromegalic, the Addisonian, etc., to recognize what we term a quantitative disorder.

There are, however, a very much larger number of cases of what we might call a qualitative type. Might there not occur the same vascular activity either under or over the normal threshold, lessening or increasing the function without actual tissue loss? In the systems mentioned previously, the nervous mechanisms appeared to be important, may be so in this system. This under- and overfunctioning, due to changes in the vascular tone, may also control the variation in the blood and tissue metabolism which is manifest in certain types of cases where adjustment takes place moderately quick. Eppinger and Hess[18] have presented facts to show that the various organs produce sympathicotropic and vagotropic impulses, which either increase or decrease metabolism. Perhaps this is most manifest in the case of the thyroid, as under experimental or therapeutic feeding of thyroid, there is an increase in the metabolism of carbohydrates. Higier[19] places the thyroid in the catabolist group.

Gley has stated: " . . . it follows that the tone of the muscles of the blood vessels in so far as it depends on an automatic stimulation, either direct or indirect, is maintained not only by nervous stimulation, variations in gases contained in the blood and by the products of the catabolic processes, but also by a specific substance normally found in various glands. . . . Many have occupied themselves with determining these functional correlations of a chemical nature, connecting them with one another and at the same time differentiating them from the correlation of the nervous origin —it was also recognized that there are still others

which form an intermediary class, the neurochemical correlations or functional manifestations provoked by the nervous system, this nervous action determining a chemical excitation, which is carried to some other part of the nervous system."

To illustrate: A patient of 26 years was married two years ago, and during the first six months she gained fifty pounds in weight, reaching 196 pounds. Her skin was coarse and rough, her hair brittle and thinned. She had practically no complaints except that she was getting too fat. Her blood pressure was 120, systolic. Her cardiovascular system was apparently negative. Her voice became harsh and cracked at times. Her blood sugar was 76 mg. It was very evident that she was not metabolizing her carbohydrates, for it mattered little what she ate she would gain in flesh. This high carbohydrate tolerance, and yet an accompanying hypoglycemia, indicated what would seem to be a loss of sympatheticotropic impulses, which might be supplied by the administration of thyroid. Such was done, and within seven days a second blood sugar showed a rise to 88 mg., with a coincident loss of eight pounds in weight and a complete change in the appearance of her skin. It became soft and moist, and she said with regard to herself, "I feel so much different."

Could this increase in catabolism not go on until the sugar content reached beyond the threshold of normality, and produced a hyperglycemia with a concomitant glycosuria? Over-determination undoubtedly can exist in an endocrinopathy as well as in a psychopathy; and should be kept before one's attention in regulating metabolic functions. No doubt symptom-complexes directed towards the various glands do occur spontaneously at different times in the same case (Farnell[20]), but this is an inherent physiological adjustment. The former, however, is probably the over-determination of the clinician and the pleadings of the patient to be thin. It is quite evident that thyroid feeding for the purpose of reducing weight should be governed by the blood

chemistry in relation to carbohydrate metabolism, and that this factor should be recognized as being fully as important as the patient's appearance and general feeling, if future mishaps are to be avoided.

Mention might be made at this point of a case in which the cardinal complaints were connected with the cardiovascular system.

The patient is a young man, 27 years of age and single. From the age of eight, until twenty-one, he was subject to convulsions, occurring only at night. In appearance he was slight and not overweight. At 21 years a distinct change took place; his seizures stopped temporarily; he grew stout; hair appeared all over his body; he became hyper-sexual, vigorous and overactive. When seen, eight months ago, his weight was 170 pounds; he had a heavy growth of hair upon the chest and abdomen; he sweat profusely; his blood pressure was 168 mm., and his pulse 130, irregular and skipping; he had a systolic blow at the apex; he was nervous, restless and overactive. By toning the vascular system his pulse rate dropped to 88, the blood pressure to 136 mm., and his general nervousness subsided greatly. He then had a period of sexual impotency, during which time ideas of reference and feelings of being under suspicion developed. He felt the opposite sex looked at him and he was self-conscious, fearing that they might know he had had convulsions. This psychical impotency and the accompanying defensive mental state of a mild paranoid type became adjusted within a few weeks.

This case is not unlike the pluriglandular syndrome as seen in the adrenal-pituitary group, and yet the adjustment has taken place largely through the balancing of the neurogenic mechanism of the vascular system, apparently.

THE VEGETATIVE NERVOUS SYSTEM

The next system to be considered briefly is the autonomic or vegetative nervous system.

Eppinger[18] has called that system which supplies the smooth muscles, cardiac muscle, and glandular tissues

the vegetative nervous system, because through it the normal continuation of life and the vital functions are preserved. On the other hand, the better known "sympathetic nervous system" is that portion of the vegetative system which is represented by the gangliated cord on either side of the spinal column, with its ganglia and communicating fibres, which might be termed the "thoracic autonomic." The vegetative system proper is divided into the midbrain, whose segments pass by way of the oculomotor nerve pathways; the bulbar, which through the facial, glossopharyngeal, and vagus supplies the glands, vasodilators of the head, heart, bronchi, esophagus, stomach, intestines and pancreas; and the sacral, which supplies the descending colon, sigmoid, bladder, and genitals.

Concerning these different divisions, the midbrain, bulbar, and sacral are similar in that they are entirely local in their supply; whereas the sympathetic or "thoracic autonomic" not only has its local distribution, but also it sends segments to the same structures as the other system, thus causing the vegetative system to be innervated by only one system. As examples of autonomic structure having a double supply one may mention the salivary glands, gastric glands, intestinal musculature, heart and blood vessels. Those having a single or sympathetic supply are the smooth muscle of the skin and the blood-vessels of the intestines, and the internal generative organs.

As an example of the antagonistic action of the two systems one may instance the external genitals. As an example of double innervation of similar stimulating effect, the salivary glands, in those nerves having a vegetative activity, the efferent and afferent fibres are interrupted in their course from the corticospinal system by preganglionic and postganglionic segments, with a variation in location from the sympathetic cord to the submucosa of the intestines. This latter nerve

supply has been called by Langley[21] the "enteric nervous system" and it governs the entire tract from the esophagus to the rectum. He mentions the fact that the character of their connections with the autonomic system and their control of the gastroenteric tract is little known, but that they seem to have an action independent of the central nervous system. This has been ably proven by Cannon[22] in his experiments, and he concludes that when this canal is entirely separated from the central nervous system it has a remarkable power of developing an independent tonic state, that is, it soon recovers its tone. This shows that it supplies the resiliency that causes the state of tension when the canal was filled. This tension is the occasion for the contraction of viscera, which are walled with smooth muscle, holding a nerve plexus. That this tonicity is fundamental is accounted for in the failure of efferent motility in atonic states.

It is a common observation that tonic contraction and rhythmic peristalsis disappear in asthenic and exhaustive states, and Cannon's conclusions agree with these observations that anxiety, morbid fear, worry, mental distress, and kindred disorders lessen or stop gastroenteric movements, and decrease or abolish the tonus of the alimentary canal.

There is still considerable difference of opinion as to the make-up of the afferent nerves of the vegetative system. Some investigators believe the afferent nerves contain somatic fibres, and yet, if so, why should there be a difference in their functional activity? It is well-known when pain is experienced in the viscera that it is usually due to a mechanical cause, and its action upon the body is, as Head terms it, reflex. This has been shown by Sherrington[23] to be due to an elevation in the threshold of the excitability of the arc in the viscera. This difference also is extended centrally in that antonomic afferent fibres have no central connection,

whereas somatic fibres have a connection in the brain cortex.

This intimate relationship with the cerebrum and the emotional life is found in many types of disorders—the individual leading purely a vegetative existence, as seen in the mentally defective child, the adult in a state of mental deterioration. The profound epileptic shows the loss of control of such impulses as inhibit the function of the salivary glands, the sweat glands, the intestinal tonus and vascular stability. The sweating and drooling, the low-tensioned pulse, the intestinal spasticity are not uncommon symptoms in the praecox, the defective, the epileptic. In the praecox there is an emotional blunting, in the defective a lack of development of normal emotion, and in the epileptic an instability of the emotion. In lesions of the caudate and lenticular nuclei, among the most prominent symptoms are the emotional outbursts (Mills[24]), Wilson[25]). This would seem to point towards a disturbance in the passage of impulses from the cerebrum via the basal ganglia and probably through the sympathetic system.

EMOTIONAL ASPECTS OF ENDOCRINOLOGY

Disturbances in the threshold of emotion are not uncommon in the quantitative disorders of the endocrine glands—the stolid, non-responsive hypothyroid; the excitable, unstable hyperthyroid; the sensitive and touchy adrenal; and the apprehensive and depressed ovarian type. In these individuals their emotional life plays an important part in enhancing the visceral symptoms. They have a weak, affective tone, and do not respond or adjust themselves to the ordinary problems of life. When unavoidable experiences occur one must expect a profound visceral reaction, the type depending upon the system so-called "conditioned." Nervous reactions will become manifest through dermal activity, digestive upsets and cardiovascular disturbances. That these in-

dividuals are merely considered "nervous," one is quite aware and the real basis of their trouble is passed by. A nervous disorder, however, should convey immediately to one the idea of a state of restlessness, unhappiness, dissatisfaction, poor adaptation, which contains as its underlying condition a conflict in the inner psychic or psychobiologic harmony.

The exact location of these higher brain centres is still a matter of dispute, and yet there is evidence that it has a close connection with the chromaffin system, which it may be recalled is really a collection of endocrine structures. The most essential parts of the chromaffin system are the nervous or posterior lobe of the hypophysis, the sympathetic ganglia and paraganglia of Kahn, and the nervous elements in the adrenals. This specialized nervous tissue has also been found embedded in the kidney, and even carried down with the ovaries and testicles in their development and descent.

Functionally, this system produces in the granules of these cells the hormone adrenin. Exception has been taken to recognizing the adrenals as internal secretory organs because [Kahn] the chromaffin cells do not conform to the type of epithelial cells nor their grouping to glandular structure, yet from a physiological viewpoint the internal secretory conclusion is quite justified. What can be the significance of this intimate association between the glandular and nervous elements?

The production of adrenin in these cells is now an undisputed fact. It enters the blood stream via the vein directly. This product acts upon certain tissues and increases the activity of metabolism.

A young girl of 15 years was frightened by the sudden appearance of a burning mattress passing the window, in which she was sitting. This fright, with later lack of sleep, produced a mental reaction not unlike that seen in schizophrenia. The systolic blood pressure was reduced to 90 mm., the pulse rapid and low tension.

There was a thyroid enlargement and cessation of menstrual function. Mentally she was slow, inactive, lacked initiative and *rapport*. She lost weight, and her skin was oily and wet. She ate little, and her bowels were constipated. She had been a bright and active child, had stood well in her studies at school and had plenty of chums and social duties. This was all changed. There were no shut-in symptoms prior to the fright. She was looked upon as a case of adrenal dysfunction, brought about through a "conditioned" sympathetic system exaggerated by an emotional trauma. Within a few months, during which suitable measures were instituted to spare and support the adrenals, adjustment has taken place with a return of all normal physiological activities; but the emotional life, which was considered normal before the trauma, is now somewhat over-determined, with a tendency to exaggerate social contact.

One may observe in his clinical work the many factors involved in arriving at a diagnosis of a qualitative disorder referable to the endocrine system. It is common to be asked if such and such a case is not a pituitary or a thyroid case, and to be told that mixed glandular products have been tried without avail. When the case is investigated a disturbance in instinctive demands may be of primary importance, or an emotional maladjustment, or even an environmental maladaptation. These endogenous and exogenous factors do indeed play a part in disturbing the neurogenic control and do undoubtedly bring about disturbances in function not only referable to the skin and mucous membrane, to the cardiovascular system, but also to the endocrine system, and disturb their function with possibly a resultant disorder in metabolism. Many such cases undoubtedly adjust themselves, others require aid, as organotherapy, and some even go on to actual tissue loss and cessation of function with its concomitant interrelative disharmony.

It is hardly within the power of a clinician to be able to go deeply into all factors in all cases, as they pass

by in the rush of a day's work, but it would seem that in addition to the objective clinical picture an analysis of the personality, an investigation into social and environmental activities, a study of the instinctive demands, and a determination of the level of the emotional threshold would be helpful in the prognostication of so many of these qualitative and pre-quantitative endocrine disorders, especially those in which the nervous symptoms predominate, and which, unfortunately, heretofore have received such limited attention. In truth, success will always attend those efforts which go beyond the ordinary methods of procedure, and it will surely be an advantage to him whose conception is broad enough to comprehend the disorder in the broadest aspect.

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IV

ENDOCRINOLOGY IN EVERY-DAY MEDICINE

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Internal secretions are chemical substances organic in nature, elaborated from the food we partake of by certain structures within our bodies, called the ductless glands. These secretions enter the blood stream, and each exerts a certain definite, constant influence upon the general economy and well-being of the organism.

We very often wonder why individuals living apparently under the same surroundings, and partaking of the same kinds of food in the same quantities, still differ widely in their external and internal make-up, *i. e.*, in their external appearance as well as in their disposition, temperament, general strength, etc. Some individuals are always very thin, no matter how much and of whatever rich food they eat; others enjoy pretty fair development of body tissues; and still others suffer from an excessive deposit of adipose tissue in their bodies. Some people are undersized; others are of a height proportional to their weight and thickness; and still others are very tall, altogether out of proportion to the other measurements of their bodies. Some individuals are exceptionally cool-minded, and comparatively passive to external impressions and to changes in their life; others are fairly well-balanced in their emotional feelings; while still others are of an extremely nervous temperament, and respond to similar impressions in an unusual, excessive and, therefore, abnormal

manner. Some, again, are very optimistic in nature, others are very pessimistic, and so on.

What is it, then, that accounts for all these differences in individuals, who, according to the character of their external surroundings and mode of life, rather should make up one single type?

It is logical to assume from the above observations, that the factor or factors responsible for the above-named variations must reside within each individual organism itself, and not outside of it.

Now, which of the many structures making up the complex human organism logically may be held responsible for the above-named variations or deviations from the normal in size, shape, general development, nervous disposition, temperament, and of many other attributes, mental and physical, of the human mind and body?

The functions of the majority of the organs of our body are now fairly well known to us and understood; and, as far as we know and understand them, we have no reasonable ground to make them responsible for the above-mentioned differences or abnormalities. Besides, in every-day medicine not infrequently we encounter patients with complaints or symptoms referable to some certain mechanism of the body, whose function under normal conditions we well know, and the pathology of which we can make out after it has progressed sufficiently to bring about the usual symptoms. Thus, tachycardia, arrhythmia, dyspnea, extreme nervous irritability are not infrequently the causes that bring patients under our observation; and, in spite of careful repeated examinations, we fail to find anything wrong with the organs, which are actually engaged in the processes of circulation, respiration, or mentality, so that we must exempt the respective organs from any direct responsibility for the above-mentioned abnormal phenomena.

But there is a group of structures in the human organism whose functions are not as well understood, because their activities are not as readily observable under normal conditions. We do, however, recognize definite changes produced in the well-being of the individual by a hypo- or hyper-function of one or more of these structures. They are the so-called glands of internal secretion, including the hypophysis, the thyroid, the parathyroids, the thymus, certain parts of the pancreas, the spleen, the adrenals, the ovaries, the testicles, the prostate and perhaps others. It is these structures to which our attention should be directed when we think of the above-mentioned phenomena.

Especially must we concentrate our investigation on these structures as being the possible cause of the trouble, when conditions, such as have been mentioned above, become marked in the absence of any chronic infection or affection, such as tuberculosis, chronic kidney disease, organic heart disease, etc.

In all such or similar cases the first step toward a rational treatment is to correct errors in diet as well as in the mode of living, and to remove all sources of infection, if such be found and their removal is possible.

If these hygienic measures fail to bring about an improvement in the condition, it is only logical to assume that some one or more of the glands of internal secretion are at the bottom of the trouble; and then we must, by virtue of necessity, turn our attention to these glands and try to find out which particular gland or glands are at fault, and also to determine the character of the fault, *i. e.*, whether they are secreting too much or not enough for the organ. We can then institute our treatment accordingly. In cases of the first instance the oversecretion will have to be checked, either by drugs tending to inhibit such action, or by the removal of a smaller or larger part of the gland in question. In the second instance, the administration of the active

principle of the gland in question, obtained from the domestic animals, is indicated.

While it is true that our knowledge concerning the glands of internal secretion is far from being complete, we know enough about some of them, at least, to justify our attempt at this organotherapy with a double purpose in mind, namely, to try to relieve distressing symptoms and complaints, and also to promote, at the same time, our knowledge about the matter.

Thus, the rôle that the thyroid gland plays in controlling or supervising the metabolism of the body by balancing the processes of destruction and reconstruction of tissues, is well known to all who read standard works on physiology. Equally well we know the function of the corpus luteum, manufactured by the ovaries, in controlling the process of menstruation, and in balancing nervous irritability. We also by this time know the rôle played by the adrenals in maintaining the tonicity of the heart and blood vessels, and, indeed, of the musculature of the human body in general.

It is not necessary here to discuss the physiology of the endocrine glands in detail. It will be sufficient for us to admit that we know enough about them to put this knowledge into therapeutic action on a rational basis.

THE RELATIONS OF THE GLANDS

Right here the attention of the reader must be called to the following logical consideration: As in any complicated piece of machinery one part out of order for any length of time will necessarily interfere with the proper function of some one or more other parts, with which it is closely related. So it is with the endocrine glands. They are so closely interrelated with one another that the improper function of one of them will bring about a derangement in function in one or more of the others.

We must bear this in mind whenever we desire to institute organotherapy, and see that the patient is supplied with *all* those principles of internal secretion that his organism possibly may be in need of.

It is to be hoped that the advances in physiological chemistry will provide us in the near future with certain means for the detection of the different principles of the internal secretions in the blood, for they must absolutely be in order to exert their influence on the organism. At that time we will also be able to diagnose precisely which particular gland is causing the trouble in a given case, as its comparative hypo- or hyper-activity, for then we shall be able to demonstrate its dysfunction in a scientific manner by determining a decreased or increased amount of its active principle in the blood. But until this is possible, we must have recourse to the method known as pluriglandular therapy in order to give the organism a chance to select and make use of what may be lacking.

Occasionally we find cases where the deficiency of a certain single gland is well manifested, and in such instances monoglandular therapy directed to the one gland in question largely fulfills the indication.

The following cases, some of them still under my observation, have convinced me of the efficacy of the glands of internal secretion as therapeutic measures in certain instances.

CASE NO. 1. A young man of 26, fairly well developed physically, and a butcher by occupation, consulted me for extreme weakness. About 2 P. M. he said he is all played out, although he never works very hard. His family history and past medical history are negative. The physical examination revealed nothing abnormal except that his blood pressure was remarkably low for his age, the systolic pressure being 100 mm. and the diastolic only 55 mm.

On the assumption that the patient was not getting enough of the adrenal secretion, the dried adrenal

gland was administered. The patient is now feeling much stronger and his blood pressure has risen to 110 systolic and 70 diastolic. He is still taking treatment under my observation.

CASE No. 2. A young girl of 18, complaining of attacks of nervous spells, consisting in uncontrollable movements of the upper and lower extremities, and other parts of her body, accompanied at times by laughing, but most of the time by crying with tears. During the attack, the patient experiences a sharp pain in the epigastrium and a sensation of dizziness. No foaming at mouth or involuntary discharge of feces or urine ever occurred during an attack. This trouble began about one year ago, and was accompanied by a change in her menstrual function. Her menses, previously normal, now occur every two or three months, and are very painful. The nervous spells, as the patient calls those attacks, occur from one to several times a day, and may be brought on by a sudden noise, or by anything hot or cold coming in contact with her body. Very often the attacks take place without any apparent cause. I have witnessed these attacks in my office while examining her for, at one time, putting the stethoscope to her chest was sufficient to bring on an attack exactly as the patient described it to me.

Considering the simultaneous occurrence of irregular painful menstruation and the above-described attacks of nervous spells as one abnormal phenomenon, due, possibly, to an insufficiency of the ovarian or the thyroid secretion, or, perhaps, both—the patient was put on a combination of these principles with gratifying results. The attacks occur now at far less frequent intervals, and the patient is able, at times, to control herself when she feels the oncome of an attack, a thing which she could not do before. She is still under observation.

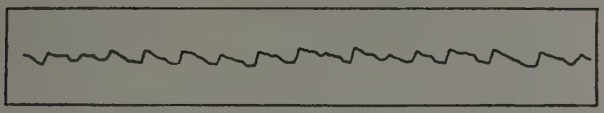
CASE No. 3. A woman, aged 32, consulted me for obesity. She is 5 feet 4 inches tall and weighs 225 pounds. She felt very uncomfortable with such an excessive amount of tissue about her body. She had been several times on a diet reduced in carbohydrates and fat, but no reduction in her body weight resulted. Exercise would only tire her out. Her urine examina-

tion showed a decreased output of urea (1 per cent.). Otherwise, it was negative.

It was evident that the destruction of tissue wastes in the patient's organism, or the catabolism, was very much below normal, as compared with the formation of tissues, or anabolism, in consequence of which the patient keeps on storing up materials, which normally should be destroyed in the processes of energy production.

Remembering the function of the thyroid gland in balancing the relation between destruction and reconstruction of the tissues, it was assumed that this patient was suffering principally from a decrease in thyroid secretion. On this ground, thyroid gland was administered. The diet was not reduced or changed. No change in pulse rate, blood pressure, or nervous irritability was noted with six capsules, amounting to 1½ gr. of thyroid extract a day for a period of four weeks, and this fact was thought to be of importance, indicating that the patient's organism was in need of, at least, that much more thyroid secretion. However, when the dose was increased to 1¾ gr. per day, the pulse rate rose from 76 to 90 per minute, and the blood pressure from 130 to 135. The patient is now taking only 1 gr. a day. Altogether, the patient has been under thyroid treatment for six weeks and has lost twenty-one pounds.

CASE NO. 4. A man 40 years of age with a negative family and previous medical history, consulted me the first time for pain in his arms, which had bothered him for several weeks. He is a tailor by occupation. The physical examination revealed a man 5 feet 5 inches tall and weighing only 110 pounds; evidently very much underweight and undernourished, with some enlargement of the right lobe of the thyroid gland. Examination of the chest revealed a very active apex beat, not displaced, but very rapid and irregular. A murmur was heard at the apex only and was not transmitted. This unusual character of the heart murmur was confirmed by several of my colleagues. The lungs were negative. A fine tremor of the fingers was noticed. Pulse rate was 105 per minute, and very irregular, as shown in the accompanying sphygmographic tracing:



Blood pressure, 170 mm. systolic, and 70 mm. diastolic. The urine showed an increased output of urea (3½ per cent.). The electrocardiogram showed evidences of auricular fibrillation and a basal metabolism test, done at the university hospital, showed that it was 78 per cent above the normal. This patient evidently presents a condition exactly opposite to that of the preceding case. Here the destruction of tissues is greater than the reconstruction, due to a hyperactivity of the thyroid gland. The diagnosis is hyperthyroidism. We do not know of any remedy that will stop the hyperactivity of the thyroid, but we started by seeking for fundamental causes for the irritation. Therefore, the treatment in this case was begun by the removal of the tonsils and all teeth that were found diseased, on the ground that focal sepsis may cause stimulation of the thyroid gland. As no improvement followed, the administration of the pancreas substance is indicated, as it happens that this gland is believed to counteract the thyroid gland in its action upon the heart. Should the pancreas therapy fail, recourse to the X-ray or partial thyroidectomy will be indicated:

Many other instances might be mentioned, but the above are referred to in order to emphasize the importance of endocrinology in every-day medicine, and to call attention to the encouraging therapeutic possibilities that this new knowledge offers to the profession.

The more we study the ductless glands and their hormone control of the body, the better are we able to discover the common disorders, heretofore overlooked, which really are due to dyshormonism, as it has been called; and to add to our usual treatment suitable organotherapeutic regulation of the disturbed glandular function.

V

THE INTERRELATIONSHIP OF THE INTERNAL SECRETIONS

By R. J. Stroud, M.D., Douglas, Ariz.

The effect of impairment or removal of certain endocrine glands has been known for many years, but their relationship to one another and to the whole series of internal secretions produced has been neglected until very recently. For many years before Brown-Séquard's work the subject of endocrinology was either in disrepute or considered of no particular importance. All of the textbooks on physiology were barren of the subject except in a cursory way. All had recognized the effects of castration on both young and older subjects, but when the subject was first revived by Brown-Séquard's remarkable report (in 1889), the stimulus was killed, as charlatans found their pocketbooks enriched by the advertising of gonadal substances about which the whole profession was talking. History has a habit of repeating itself, and this same thing seems to be happening right now.

When real charlatans use any method unscientifically the profession, as a whole, condemns the procedure, whether there is any merit in it or not. It is then forgotten until revived. The more recent interest in "monkey gland" treatment is simply a revival of the work done in France some thirty years ago. It is within the memory of a great many physicians that iodine fell into disrepute when the laity began extolling its virtues, but it has revived in greater measure than

ever, especially in the fields of surgery. The medical profession has to be one step ahead of the laity or it is very likely to condemn the subject in question; but in the course of time, practical scientists insist on the reintroduction of anything really useful and scientific which will benefit mankind.

That the internal secretions and their possibilities are now being widely recognized is patent even to the prejudiced, and this in spite of untoward publicity in the press. One of the most prominent of the world's medical weeklies has for the past few months been including in its leading papers pithy articles on the subject (1).

One cannot go very far into the study of the internal secretions without being struck with the fact that there is a possibility of the endocrine glands having some close relation to one another. Physiology has demonstrated beyond a doubt that in the functioning of the digestive secretions certain "hormones" are necessary to maintain the balance and provide certain stimuli to the glands producing these secretions to maintain quality and quantity at normal (2). The fact that a hormone may augment a mental stimulus is more or less simulated in the fact that a man's well-being depends as much upon the endocrine balance as upon mental stimuli that have no particular relation to endocrine function. The mental stimulation in both cases is more or less fleeting while the hormones and internal secretions have to "carry on." It is a coincidence that Starling should have given such a stimulus to our present-day conception of endocrinology and to have coined the term "hormone" in relation to the digestive stimulation (3).

Although the relationship of certain endocrine glands with one another has been demonstrated these many years, it is only in the last decade that the

interlocking of their functions has been fully established. Since 1858 it has been shown that there is a distinct relationship between the thymus gland and the testes, removal of the thymus hastening a maturity and development of the testes, and removal of the testes causing a persistent growth of the thymus (4). The relationship between the ovaries and the growth of the mammary glands, the ovaries and the thyroid, the thyroid and the parathyroids, the pituitary body and the mammary glands has merely demonstrated that endocrine dependence does not cease with any two individuals or sets of glands, but that all of them are more or less interrelated. This fact has demonstrated the clinical importance of augmenting any depletion or derangement of certain endocrine organs with other associated secretions.

While resting an overworked organ by adding its pabulum artificially, it is also equally necessary to encourage the organ to further secretion. This stimulus not only comes from replenishment through its own pabulum, but is augmented by the other secretions which have independent but none the less related actions. Only in this way can a true balance of function be secured. In other words, there evidently is a hormonic exchange of stimuli between all glands as well as an "autohormonic" stimulation. When this interhormonic balance is as it should be, and the relations between the endocrine organs are correct, there is a feeling of well-being even when so-called vital organs may be diseased. Thus in pulmonary tuberculosis, when there is a good endocrine balance, the patient has a hopeful and normal attitude towards life in general; while in individuals with low blood pressure, resulting from adrenal depletion, the patient feels hopeless. This was generally true following the late influenza epidemic. To illustrate the above, the following case comes to mind:

Male, aged 41, height 5 feet 8 inches, and weight 119 pounds, gave the history of dysentery three months previous, which was severe. He was ill in bed two months, and since that time had been under the care of a physician who had prescribed tonics by mouth and had also given them hypodermically. Despite this treatment he had not gained in weight and his mental attitude was hopeless, as he wanted to take out some life insurance and knew his physical condition would be against it. Examination showed all organs normal except the apex beat, which was "soft." The blood pressure showed the cause of the trouble. The readings: Systolic, 105; diastolic, 80 mm. The stimulating tonics were discontinued and a pluriglandular formula was given for two months. At this time the systolic pressure was 127 mm., and he weighed 147 pounds.

His despondency has now left him, and he has not yet, after one year, taken out life insurance. The necessity of "protection" for his family left him as soon as the well-being was restored, due to the reestablishment of the normal endocrine balance. He also stated that his libido had been increased, which demonstrated the broader effect of the stimulation from the pluriglandular extract.

Nature, by selective action, always tries to maintain the endocrine balance. If one organ is impaired the co-operative selective action of the other glands helps to keep the balance by making use of the allied secretions where possible. At other times the function of other glands is increased to make up deficiency. If this close relationship were not maintained, the balance would be very easily shaken and comparatively slight disturbance of any of the organs would lead to noticeable clinical symptoms. The results of endocrine underproduction or overproduction would be felt immediately. This hormonic action of one gland upon another is in relationship with all glands, whether these glands produce endocrine substances which augment their action, or whether they counteract it. Only in

this way can this balance be explained. For instance, an increase of the thyroid secretion does not always manifest itself immediately. Some time elapses before clinical signs develop, and even then the basal metabolic rate is often maintained. Without increased action of other glands, stimulated by the presence of thyrotoxin, all cases of thyrotoxic adenoma would show disturbance of metabolic rate immediately and constantly, which is not the case. In such cases an excessive stimulation is given to the adrenals, for in these adenomata the first sign is often a rise of blood pressure (6). This stimulation is kept up until balance is definitely lost, and then the clinical symptoms manifest themselves. The balance is lost only when the other associated glands cannot keep up with the abnormal gland. Then the picture is not only that of a predominating thyrotoxic element, but an augmentation of symptoms through overproduction of other internal secretions, notably the ovaries and adrenals (7).

At times this interrelationship is hard to determine except empirically, but the hypothesis is well borne out that in cases of hyperthyroidism the balance is not only kept for some time, but the feeding of cooperative endocrine products, like thymus, adrenal or pituitary extracts, seems to alleviate symptoms (8). After the stage of high blood pressure comes myocarditis through loss of muscle tone. Here the stimulus to adrenals and pituitary has been so great that they have become exhausted. This exhaustion of the adrenals makes it ofttimes necessary to give treatment with adrenalin before the operation for thyroidectomy, in order to improve the heart tone. For the same reason after-treatment, this time with adrenal substance, following severe cases, has to be long-continued because of this exhaustion (9).

That this hormonic action and interaction is constant and necessary, and that development of some glands

depends on the secretory activity and stimulation of others, is shown by the fact that in hypothyroidism in children there is slow growth and development. Also in hyperthyroidism it has been found that the most severe types often are accompanied by enlargement of the thymus. Retarded sexual development and quick, prolonged growth before maturity is also coincident to enlargement of the thymus and feeding with the extract (10). Then the anterior lobe of the pituitary body has also an effect on growth, abnormal amounts producing giantism or acromegaly, while a lessened production retards growth and maturity. The feeding of tadpoles with thyroid gland produces dwarfism but quick maturity, which is the direct opposite of the results of experimental thymus feeding.

These facts show that it is hardly possible that a single gland can be at fault in metabolic disturbances, but that the hypothesis must be accepted that a great many internal secretions enter into the equation. Clinically there has been decided improvement in certain backward children following therapy with a single extract, like pituitary or thyroid. Even then it is more reasonable to suppose that both are more or less involved in the disease [and that pluriglandular therapy is even better.—H.R.H.]. The reason for the improvement is that the feeding with pituitary extract adds its hormonic influence to the thyroid and thereby stimulates its production, and vice versa. Other influence is also felt, as the rest of the glands are also stimulated to secretion, for the output of adrenin is enhanced, which can be seen by the rise in blood pressure, which is practically always low in cretins.

The maturing of the sexual glands also follows the introduction of the above secretions. The feeding of one gland having such a marked effect on the whole has led us into the error of classifying endocrine disease as due to the disturbance of a single gland, and

prescribing a single organotherapeutic product, whereas, due to the deficiency of one, all are below par, as they have lost the stimulus which they get from one another and which also stimulates themselves, no matter which gland was at fault in the beginning. In fact, as to whether a single gland was at fault even in the beginning, is not above question (11). Time and further clinical experiment will show these relationships more definitely, *i. e.*, that there may be a possibility of measuring the exact amount of stimulus one gland has on all of the others.

At the present time we know that certain deficiencies affect the well-being of many individuals, and that overproduction does likewise. Brown-Séquard noted the difference on himself by the ingestion of gonad secretions, and being a pioneer, did not perceive at the time that he not only replaced gonad substances, but stimulated the production of new endocrine substances by autohormonic influence. [Hallion calls this "homostimulation."—H.R.H.] His feeling of well-being and ability to perform tasks which before were considered impossible, was due to more than the increased gonad function. His experiments show that the influence of the secretion of the Leydig cells on some of the other endocrines is very great. Had the stimulus been given to the sex glands only there could have been only an increase in sexual power, whereas, he mentions more the power to stand physical strain and sustained mental exertion; for sustained mental exertion itself has an effect both on physical power and the testes.

Before maturity the influence of the gonads is small or absent, but once it is developed it must impart certain stimuli to other endocrine organs which they afterwards need to maintain the balance. If this were not so, the so-called pituitary eunuch, or other men who have become impotent, would not waste lavish sums to regain this libido, while the true eunuch, who was cas-

trated before puberty, is not exercised about his condition. In the former is a despondency and lack of force caused by the crying need for these stimuli, while eunuchs often have buoyant dispositions and are raised to places of power and trust (12). The same parallel is seen in most women following or during the menopause, where nature, or the internal secretions, are below par until adjustment is made between the endocrine organs without the ovarian stimulus.

Just as it is difficult for the internist to think of a pure type of infection, so it is hard for the endocrinologist to think of a single type of endocrine disturbance. The makers of vaccines and the developers of new ideas along this line take this fact into consideration, while an autogenous vaccine contains a definite proportion of various organism, according to the bacterial count. It is very seldom that a single organism can be blamed for all of the symptoms. Much less then can the endocrinologist think of a disturbance of a single gland because one is a dominant factor.

Having established the relationship of various glands, the application of this knowledge to clinical cases becomes of importance. The first principle to be adhered to is that of balance. To determine a balance of internal secretions each case must be approached according to the symptom complex, bearing in mind that many organs may be involved in the process. For instance, in cretinism: we have here a hypofunction of certain glands and need to make up the deficiency. We give them certain substances secreted by the thyroid, pituitary body and adrenals. As this is the purest approach to a single endocrine disturbance and thyroid function is not often present at all, thyroid substance will have to be given in greater proportion than the other glands. Better than the secretions themselves is to give standardized macerated glands which, no

doubt, carry side chains of influence, much as nux vomica has other influences than strychnine.

What has been accomplished by applying this knowledge? First, there is a quick making up of the elements necessary to restore the balance. No matter if the thyroid gland is most at fault, its stimulation on the other glands is no more necessary than the antostimulation of the others. Both synergists and inhibitory glands are stimulated to arrive at a balance, and the normal is approached more quickly if the secondary chain of glands is not far below par. When this is accomplished a single glandular extract (of thyroid, in the instance under discussion), will have to be given to keep up the balance, as this action cannot be restored in a gland that is absent or has never functioned.

Further along in life we meet those cases which, while not actually myxedematous, are below par and in whom the ovarian response is below normal, due to lack of the thyroid principle. Here again a compound formula is preferably given in the form of an ovarian extract to make up deficiency and add its quota of autostimulation, which is supplemented with the well-known synergists or gonad function, thyroid and pituitary substance. When a balance has been established the chances of keeping the balance are greater than before, as the thyroid now has the synergistic action of the ovaries. This deficiency gives rise to general lassitude, scanty menses, and nervousness. Often also there is chlorosis, dysmenorrhea and a tendency towards epileptiform attacks, simulating petit mal. The effect of a balanced extract is illustrated in the following case history.

Miss M. N., age 16. A large, well-developed girl with some surplus flesh and no evident pallor of cholorosis, presented herself complaining of nervousness* and a tendency to fainting spells. These attacks were almost like a petit mal and alarmed her mother. It was noted

that they came on mostly at the time of, or just before, the menses. There was no history of a blow on the head or a fall, and she has been perfectly healthy until two years ago. The nervousness was increasing, there was no prominence or enlargement of the thyroid, the urinary examination was negative. The mammae were large and highly placed.

She was given iron and arsenic, and some elixir or triple bromides to be taken at times of worst nervousness, and told to report at some future date. She reported much improved but not entirely relieved. Four months later she had a return of the symptoms, and with an accentuation of the "nervous spells." The mother was afraid to have the girl go out alone. A diagnosis was made at this time of thyroid and ovarian insufficiency and the patient put on a pluriglandular combination.

In two months the nervousness had disappeared, the menses were increased and not so painful. More medication was sought and since that time (two more months), there has been no return of the symptoms.

Applying the same thought to a later period in life we see the various phenomena of the menopause with the same nervousness*, but with a tendency towards menorrhagia more often than not. The former usual treatment was to give tonics like I. Q. & S. and variants. (While this treatment is empirical, more or less, it is not so unscientific as is generally supposed because of the stimulus given to the endocrine organs by certain drugs. Iodine and its action on the thyroid is generally known and arsenic has an action especially on the hemopoietic organs.) The stimulus is insufficient when drug tonics are given, and the alleviation of symptoms is temporary and often practically nil.

The same chain of organs is again at fault. This time the stimulus of the ovary has begun to fail, where it has played a large part in the economy and established, since the time of puberty, a new balance. The thyroid gland and ovary seem to need each other especially to establish and maintain this balance, which

makes it hard to determine which is primarily at fault. It often takes the other organs three years to accommodate themselves to this important change, and in the meantime the balance must be helped. The same combined extracts that enter into the normal sex stimulus here make up the deficiency. It has also been my experience that the menorrhagia is controlled in most cases where there is no sign of tumor growth; and while roentgenology has a place in the treatment of these menorrhagias to control the hemorrhage, it merely hastens the process of the menopause and does not help the nervous symptoms altogether. In fact, these are sometimes increased because the shock of quick withdrawal of the ovarian hormone influence is greater. Endocrine treatment should be given a trial before roentgen exposure is advised, and when this is done organotherapy should be used in conjunction with it to help the balance. The following two cases illustrate the action from endocrine treatment, especially balanced treatment:

Case 1. Mrs. E. E., age 41 (a relative) called a physician to her home for "flooding," which was accompanied by nervousness which had been "coming on lately." He paid little attention to her lament and said that all women had it to go through, and showed such little attention that another physician was called in. Various agencies were called into play including ergot and vaginal packing, and an examination revealed a tumor that was causing the trouble, augmented, presumably, by the menopause. In time, an operation was performed. This was not satisfactory, as the surgeon gave an opinion that it was impossible to remove the tumor because of its being in such close relation to the large pelvic vessels. He told the patient that he had tied off some of the tumor vessels which would help it to absorb. In due time the tumor was found to be absorbing and then the patient was referred to a roentgenologist to assist in completing the absorption. Many treatments were taken, and more were recommended, but the patient believed she did not

need them and discontinued. All this time the nervous symptoms were present and she was told that all women went through it, but that violet ray exposures would help. At this time she wrote to the author and was put on a combined extract as above described. In two months the nervous symptoms had disappeared and have not returned for one year. Treatment was persisted in for four months.

Case 2. Mrs. E. L., age 42, has had nine normal children and no miscarriages, and always felt well until a short time before presenting herself for examination (November, 1918). Past history negative.

Present History: Had missed menstruation several times in the past year and the last few times "flooded terribly" when menstruation came; has not felt well and been nervous and weak, especially of late; has lost the interest in home she used to have; blood-pressure S. 130, D. 92. Adnexa were normal and there were no signs of fibroids or malignancy.

"This patient was given corpus luteum for two months and as a result she felt a good deal better, and she had begun to think her troubles were over when she had another attack of menorrhagia. This was severe. As they lived 25 miles away the husband came alone as he did not wish to aggravate the hemorrhage. This time the combined extracts were given but were continued only 33 days, as she felt so much better. There was no report until June, 1920, when the husband again reported a 'slight show' and for the last month some nervous symptoms. Again the same combination was given with prompt clearing up of all the symptoms until the last report, a week ago, at which time the same treatment was advised for another month."

These few case histories are but a meagre offering to the clinical side of the results of study of the close relationship of the internal secretions. The cases are picked at random and offer additional evidence of the importance of the endocrine balance in clinical practice.

Man is not a well or normal being when his endocrine organs are not properly balanced, and his feeling of

well-being and efficiency are impaired until that balance is restored. This is true whether the balance between the endocrine organs themselves is at fault or whether the balance between these organs and the rest of the body is impaired.

The imbalance manifests itself in certain physical or mental symptoms, and often both. We cannot consider balance without thinking of the relationship of the endocrine organs as a whole.

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VI

THE ENDOCRINE ASPECTS OF OBESITY

By J. W. Neville, M.D., San Francisco, Calif.

The most firmly established relation between obesity and endocrinology is the well-known ability of thyroid extract to reduce weight. When first introduced into therapeutics in 1894 by Wendelstadt[1] in Germany and the next year by Buquin[2] in France, its adoption by the profession was purely on empiric grounds, but proving so effectual and producing such pronounced results, its use soon became widespread. This popularity was not without bad results, for the effectiveness of the remedy soon recommended it to those unacquainted with its use and ignorant of its dangers. No greater prostitution of modern scientific knowledge exists in medicine than the indiscriminate use of thyroid extract in the "treatment" of obesity. It is to be regretted that this effective therapeutic agent has been utilized so extensively by charlatans and quacks in their proprietary "fat reducers."

A certain degree of uncertainty exists in the minds of many medical men as to the correct relation of obesity to disease. Some consider it as merely an extreme variation from the normal and object to treating patients for obesity. Others administer treatment with the idea of weight-reduction for cosmetic effects only. The latter procedure is rather outside the sphere of medical practice. (Axtell)[3] That both conceptions are incorrect becomes evident when the broader endocrine viewpoint is taken.

Obesity, like emaciation, is not a disease but a symptom. Frequently it is the chief or only obvious symptom, the others being obscure and difficult to discover. Oftentimes it is a sign only and gives rise to no complaint, other than the disquietude of vanity. To catalogue obesity then as a symptom rather than a disease, or a normal variation, lends a new aspect to the subject and permits of a discussion along broader lines.

It is necessary at the outset to determine definitely that a patient is indeed obese. This offers no difficulty in cases of extreme or moderate obesity, but is less easy in certain ones which show signs of endocrinopathy.

The customary procedure in ascertaining obesity is to take the height and read off from a height-weight chart the so-called ideal weight, or calculate it by formulae such as those devised by Broca, "Oeders of Van Noorden,"[3] making a certain allowance plus or minus for presumably normal variations. Such a procedure is incorrect for it leaves out of account individual variations in skeletal size and muscular development, the former being of special endocrinologic interest. A six-foot man with large framework and heavily-muscled may be twenty-five (25) pounds heavier than a man of equal height whose bones are small and muscular development moderate, yet he cannot be called obese. Such men, however, always exceed the so-called ideal weight.

Obesity may be defined as an excessive proportion of fatty tissue in relation to all other tissues. This normally is one-twentieth the body weight in males and one-sixteenth in females. This should be measured in pounds or kilos in proportion to height but must be judged in each individual case.

It is customary to classify obesity under two headings, namely, exogenous and endogenous. The former

occurs in individuals when the caloric value of the food intake exceeds the energy requirements, the excess being stored in the form of fat. The latter is seen in cases of lowered metabolism such as occurs in hypothyroidism and certain other endocrine disturbances. This distinction is brought out more clearly by a therapeutic test, it being possible to reduce the weight by dieting if the obesity is of exogenous origin, while no marked loss of weight occurs under food restriction in the endogenous type. This is illustrated very well by the following case:

Miss D. C., aged 20, 5 feet 3 inches tall, weight 142 pounds. Complaint: Constipation, headache, chilly feeling and constantly-decreasing menstrual flow. Family history negative except that her mother was very short and obese.

For the past two years the patient has been getting progressively more "dull and lazy." She is satisfied to stay at home and takes no interest in the things that used to interest her. She does not care to read because of inability to concentrate. She is not nervous, but very irritable and impatient which, she says, "is quite unlike her normal self." She sleeps well at night but awakens unrefreshed in the morning, at which time of day she feels more irritable and blue. There is a sensation of soreness in the throat which is most marked about one week before menstruation. At this time there is also a sensation of pressure and tightness in the upper chest and neck which causes smothering if she lies on either side. This seems to be getting worse the past four months.

Her periods have been becoming shorter so that she flows only two days where it used to be four or more, and the amount now is very scant. She has not perspired at all in the past year though occasionally she takes very warm baths.

Two years ago she came to California from the East and attributes her changed state to the new climate. When coming here she weighed 118 pounds. The first four months she gained 30 pounds. During a severe attack of influenza she lost 18 pounds, but very soon recovered her former weight. She has restricted her diet markedly, omitting the noonday meal and eating very little at morning and night.

Physical examination showed a moderately obese girl with placid, unanimated face; color good; pulse 72 and regular; blood-pressure, systolic 138, diastolic 70; hands were cold and dry; hair dry and lusterless; abdomen, extremities, and chest negative.

She was given thyroid extract and soon showed improvement, becoming less drowsy and more amiable. She lost 12 pounds in two months though she did not restrict her diet as much as formerly. The menstrual flow was prolonged to three days and she always perspired in a hot bath. She had to shampoo her hair oftener because of increased oiliness. The constipation was much relieved and she felt much better in every way. Objectively, she was more animated in movement and speech. The pulse and blood-pressure increased in proportion to the dosage.

THYROID THERAPY OF OBESITY

It is interesting to note that loss of weight is obtained in both the exogenous and endogenous types of obesity by the use of thyroid extract. This would indicate something in common between the two types, and suggests that the exogenous form of obesity is a metabolic disturbance also. This seems quite logical for if it is a simple mathematical problem to ingest a diet of greater caloric value than the expenditure of energy in calories, then it would be possible to cause anyone to put on weight. This we know from experience is quite difficult to do in certain cases. We also

know that many thin persons of sedentary habits who eat excessive quantities of food and apparently digest it still do not put on weight.

Obesity, of whatever type, is an expression of disturbed metabolism; and metabolism, we believe, is definitely controlled by the glands of internal secretion. We recognize that the height of the skeleton is directly under the control of several of these glands and it seems more than likely that the weight also is governed by their activity.

The problem is not a simple one, however, and requires much investigative effort. Even the relatively accurate determination of basal metabolism does not lend much aid, for investigators have shown that the basal metabolism of even very obese persons is practically normal when measured by the heat-production per amount of body surface. Those estimations that are based on the measurement of heat-production per unit of weight and which show a lowered metabolism in obesity, obviously are incorrect, for as Benedict[6] has pointed out, the fatty tissue is inert and does not affect the basal metabolism which "is a function of the total mass of active protoplasmic tissue."

Nearly every one of the endocrine glands has been named as producing a special type of obesity and we read of obesity of the genital and pituitary types or of thyroid, pineal, or adrenal origin. This has arisen through the fact that obesity often is associated with signs and symptoms which implicate dysfunction in different ductless glands. The real condition in every case is one of pluriglandular dystrophy with the obesity as a feature common to them all. The most that can be said on the subject is that obesity is a disturbance of metabolism and metabolism is under the direct control of the ductless glands. Certain of these glands are known to be concerned more directly with the metabolism of carbohydrates and fats.

The association of obesity and diabetes in its early stages is undoubtedly due to endocrine dysfunction. The mobilization of sugar seems to be under the control of several ductless glands, viz., the hypophysis and adrenals. Hyperglycemia or decreased glucose tolerance, is a frequent finding in hyperthyroidism. These facts all indicate a close relationship between endocrine activity and the metabolism which concerns itself with the utilizatioin of fats and carbohydrates.

The obesity of hypogenitalism, which is best illustrated by the eunuch, is probably secondary to decreased activity in glands other than the gonads—this lowered activity being part of a general endocrine hypofunction and the resulting cellular apathy. The obesity which is quite common in women after the menopause is also an expression of widespread endocrine hypofunction accompanied by the lowered or lost ovarian activity.

A CASE OF PITUITARY OBESITY

The unquestioned part which the hypophysis plays in obesity is illustrated in the frequent association of pathologic changes in this gland in the cases showing the clinical syndrome of Fröhlich as in the second case report:

Mrs. W. M. D., 37 years old, weight 230 pounds. Complaint: Obesity and scanty menstruation; family history negative. The patient weighed 119 pounds when married at the age of 20; in six months her weight increased to 145 pounds; the menstrual flow was excessive at times, but has been getting more scanty of late years; she has never been pregnant though she has desired children.

Examination showed a short woman, markedly obese, with heavy double chin and large abdominal panniculus of fat. There was an excessive growth of hair on the

face and body. The fingers were short and spade-like. The skin was quite moist and the hair oily.

More extensive study and examination was impossible in this case. The patient said "one doctor had tried to reduce her with thyroid extract, but it made her so nervous she had to discontinue its use."

This case was thought to be one of adiposo-dystrophia genitalis, the reports of fat occurring particularly in the locations described recently by Beck[7]. Here we have illustrated the interrelation of several ductless glands to produce the syndrome which varies in different cases as one or other of the glands predominate. This brings us to the third case report.

Mr. J. D. H., white, male, and married, age 65 years; very large man; entered hospital complaining of dizzy spells for the three days preceding; family history negative except father and mother were both inclined to be obese; no brothers and sisters.

Past history: Patient had always been obese, his best weight was 367 pounds; had taken the reduction treatment when younger and lost 101 pounds in two months; present weight, 330 pounds; history of influenza and rheumatism. At 40 years of age patient was frightened in a railway accident. Two weeks later his hair turned almost white, being formerly dark.
Systemic condition: Slight dyspnea on exertion; appetite has always been excessive; no constipation; nocturia four to five times a night; slept well until present illness; patient married but no offspring.

Present illness: Patient seized with dizzy spells, accompanied by swimming sensations in the head; no loss of consciousness; haziness of vision and what patient describes as "butterflies" in the temporal fields; leukodermal spots for past 40 years.

Physical examination shows very obese man; face florid; there are some leukodermal patches on face and neck; his hair is snow white; eyes are negative,

except the temporal halves of the disc, which are pale; the visual fields show a right homonymous hemianopsia; chest negative. Heart: Sounds distant, faint, slow but regular; no murmurs heard; pulse, 60; blood pressure, systolic 182, diastolic 68; arteries showed some hardening; abdomen very thick and panniculus; no tenderness; genitals negative. Extremities: Superficial veins dilated; slight pitting edema of legs; reflexes normal. Examination of skin of the body shows depigmentation of all areas of over-flapping skin as panniculus abdomen hangs over upper thighs. Some depigmentated areas in axilla, surrounded by areas of marked pigmentation, sharply defined; axillary hair almost absent; pubic hair very scanty; no hair on forearms or legs; normal growth on head and face. X-ray shows very small and shallow sella turcica which was found to be normal at autopsy. Blood Wasserman negative; urine negative; temperature normal.

Patient continued to have dizzy spells at short intervals with total loss of consciousness, and involuntary passing of urine. The pulse became as low as 40 to 50 per minute, with some premature systoles. A few days later patient was seized with a series of successive attacks, spastic in nature, with total loss of consciousness. His condition grew worse until death. At this time a clinical diagnosis of cerebral thrombosis was made, which later proved to be correct.

An autopsy revealed arteriosclerosis, thrombosis of the basilar arteries, chronic pancreatitis, marked obesity, fatty degeneration generalized and testicular hypertrophy. The sella turcica was found to be normal. Hypophysis was normal in both macroscopic and miscroscopic sections. The adrenals contained a great deal of fat and showed beginning softening of the center.

Several interesting points are to be noted in this case. First, the fallacy of relying upon radiograms of the sella turcica to determine the size of the pituitary and judging therefrom that the organ is functioning improperly. This case was thought before death to be an atypical one of adiposo-dystrophia genitalis, with fatty degeneration of the heart, and consequent myocardial insufficiency. Postmortem examination revealed a normal pituitary as far as morphology is concerned, but showed chronic pancreatitis and marked fatty degeneration of both adrenals. The adrenal obesity described by Gallais[8] is associated with tumors of the adrenal cortex and is accompanied by genital hypertrophy. The latter finding is present in this case, but the adrenals showed a degenerative condition, which, however, may have been a secondary process following previous hypertrophy.

The first case cited was apparently one of hypothyroidism, but the weight-reduction was only slight and the return to normal weight was not possible by the use of thyroid extract because a greater dosage than was used was contraindicated by disproportionate marked rise in pulse-rate and blood pressure. There were other factors entering into the case suggesting involvement of the ovaries and pituitary. Therapy along these lines is being followed but the time is too short to report results.

Cases 2 and 3 also illustrate the pluriglandular viewpoint, as it is difficult to state which ductless gland was responsible for the obesity. This is particularly true in case number 3, which showed signs of marked adrenal involvement, namely, early and sudden graying of the hair following emotional shock, which Cannon[9] has shown markedly affects these glands. Areas of marked depigmentation surrounded by heavily pigmented skin also points to dysfunction of the chromaffin

system. Scantiness of body hair points to hypophyseal, gonad or pineal disturbance.

In concluding, we may summarize by stating that obesity is a symptom in many endocrine disturbances, few of which are clear, clinical pictures indicating involvement of only one gland. Pluriglandular dysfunction seems to be the rule and effective therapy in treating these disturbances must take this fact into account.

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VII

A VILLAGE DOCTOR'S CLINIC

By A. Z. Hall, M.D., Eaton, Colo.

Life itself is far more fascinating than theory is about it. Observation is much more convincing than argument. Let us forget theories and arguments for a few moments and look at some real people. Just jump into my car and "make the rounds" of a few interesting cases with me. Then, after we have seen these folks, we can philosophize a little.

After the Operation, What?

First, let us stop at this beautiful, flower-embowered bungalow. The patient meets us at the door. She is Mrs. G. S., a musician, about forty years of age, the mother of one child. Two years ago she had a hysterectomy performed after repeated incisions had been made and drainage instituted for peri-uterine infection. She had been on the operating table seven times in one year. Her recovery from the operations was exceedingly slow. Nervous symptoms developed. Insomnia has been persistent and progressive during the last twelve months. She has averaged only between two and three hours' sleep per night for several months. She developed tachycardia, smothering sensations, cyanosis, indigestion and, quite naturally, despondency. She predicted the day of her death. Various physicians were consulted. "Simply nerves, my dear Madam," was the verdict. "You must learn to control yourself," they reiterated. One surgeon of repute recommended

another operation for adhesions, although he frankly admitted to the patient's husband that the operation would be largely useful for the psychic effect. Various tonics, heart-stimulants, nerve-sedatives, diets and periods of rest had been prescribed. She changed climate with temporary benefit; but after a little, the same dreary round of discouraging symptoms again presented itself. What was she to do? A neighbor tried to read "Science and Health" to her, but Mrs. S. protested that Christian Science is for those who have nothing the matter with them.

When we were called to the case, three months ago, we prescribed a thyroid-ovarian combination for the neurasthenia, a hemoglobin preparation for the anemia, and remineralization. You can see the results today. Mrs. S. is doing her own work, is sleeping normally, has put on flesh, has lost her despondency. A valuable life has been saved to the community, a delightful home has been preserved. These results are not imaginary, but real, tangible and definite.

Our next stop is at a humble cottage. Mrs. J. M. is a patient similar to Mrs. S. in many respects. She is 48 and has one child. She had a hysterectomy performed five years ago for submucous fibroids. After the operation she became increasingly morbid and nervous. She had persistent neuralgias and headaches, mild insomnia and a poor appetite. She would scarcely go away from home and asked to be let alone. She despaired of life and, at times, feared that she was becoming insane. Her friends spoke of her as being "a little queer." Patient feared she might commit suicide in one of her "spells." Bromides and other sedatives were used with but little effect. My recommendations in this case were:

(1) That all her decayed teeth should be extracted. (2) Moderate rest and a light, nourishing diet. (3) That she should receive the same ovarian combination

as Mrs. G. S., and neutralization of the tendency to acidosis or remineralization.

Let us now note the results: Her nervousness has decreased, she is sleeping better, her appetite is improved, her despondency is disappearing. She seems livelier and more friendly. Both the family and the patient are high gratified.

Give the Kiddies a Chance

Just a moment, now, while we run into this comfortable home to see two boys. They are Billy and Bobby, aged six and three, respectively. There are two older children in the family—both perfectly well. Aren't these two boys bright and active little fellows? Yes, but you ought to have seen them about three months ago. They were both fairly covered with a sticky eczema. The eruption was worse at the elbows, knees and neck. The irritation was so great that the children and parents found it almost impossible to sleep. Asthma sometimes complicated the eczema, the one increasing in severity as the other decreased. Various local applications had been tried with temporary success. Ointments, washes, dusting-powders helped for a time, only to fail in the long run. Internal remedies, from arsenious acid to lobelia, were tried in vain. Errors of diet were searched for, but we found the mother exceedingly careful to avoid giving them anything that might seem to aggravate. Plain living, cleanliness and lots of fresh air are the rule in this home. There was no blood dyscrasia that I could discover.

What could we do? We struggled with this problem for several weeks, and finally administered to each of them thyroid extract, Gr. 1/8 every second morning. Locally, we found the following of most service:

℞ Acidi Carbolici M. 10.
Ung. Resorcini Comp. oz. 1.
M.Ft.Ung.

Here are the results: The asthmatic attacks have gradually disappeared and the ezcema has entirely gone. In just two months these boys have become rosy and healthy and well.

HOPE FOR THE EPILEPTIC

While we are still at this house, the phone summons us to the pleasant home of a neighbor, J. L., a young attorney. We find Mrs. L. awaiting us with a troubled look on her face. "My husband has had another of his attacks," she exclaims, as she buries her face in her hands. "Oh, can't anything ever be done to cure him? Is there no hope for the epileptic?" she sobs. This is indeed a puzzling case. Mr. L. has consulted some of the most eminent physicians in America. He was thoroughly examined at the Mayo Clinic. His appendix was removed, "on suspicion," by a prominent surgeon. His tonsils went at the hands of a nose and throat specialist. Still his epileptic attacks recurred every four to six weeks. Bromides, nerve-tonics, rest, exercise, change of climate, restricted diet,—all were tried to no avail. What shall we do? What would *you* do?

With considerable misgiving, we decided to try another pluriglandular formula and prescribe a preparation of thyroid, thymus and anterior pieuitary, together with thorough cleansing of the bowels and a purin-free diet.

The results in this case have proved more than satisfactory. There has been no epileptic seizure since we began this treatment.

A CASE OF FLOODING

Just across the street let us stop to see Mrs. J. P., a woman of forty-six, who is going through the "change of life." She has raised a large family and has always been a hard worker. Lately her periods have been getting more and more exhausting. Frequently she loses

a pint of blood during one day. Whenever she moves the blood gushes from her until she is almost exsanguinated. No fibroids having been demonstrated, we place her on mammary extract, suitably reenforced, with splendid control over the menorrhagia, and we now find in Mrs. P. a very grateful patient.

Is She Pregnant or Not?

We must now return to the office. Here we find Mrs. H. G., a young woman of twenty-one, awaiting us. She complains of considerable pain in her neck, back and thighs, together with some nausea. The symptoms are generally better in the after part of the day. Mrs. G.'s neighbors have told her that she is pregnant; but she had her usual menstruation one week ago. She has not noticed any change in the breasts or the other usual signs of pregnancy. Being unable, from physical examination, to definitely settle the question, we prescribe a preparation of desiccated placenta, with the assurance that if she is pregnant the unpleasant symptoms will vanish at once; while if she is not, the nausea will be aggravated. This bids fair to become, in my hands, a simple and reliable test for pregnancy (1).

A Dope Fiend

Next enters the "dope fiend," F. H., an emaciated, prematurely old patient of 58, who has used "the drug" for nearly a score of years. We have succeeded in reducing the daily allowance from four grains to 3/4 gr. and find considerable advantage in building up the depleted bodily powers by applying the principles of adrenal support, which deservedly are becoming better known and more popular.

High Blood Pressure

Here is Grandpa M., a man of 68. Arteriosclerosis has raised his systolic blood pressure to 248. By means of rest, dieting, Epsom salts and small doses of thyroid

(gr. 1/8) we have reduced the pressure to 206 in just ten days' time. "How are you today, Grandpa? Feeling better? That's fine. You seem more cheerful and optimistic, I'm sure."

CHEATS THE SURGEON

Mr. H., a middle-aged professional man, is the next patient. He is somewhat under normal weight, and informs us that a few years ago he suffered from an attack of incipient tuberculosis. He feels somewhat depressed at present and complains that he cannot concentrate upon his work. The urinary analysis is negative. Chest-sounds do not seem to indicate any tubercular activity. Upon palpating the abdomen, slight tenderness is elicited in the region of the gall-bladder. The bowels are sluggish; stools hard and foul-smelling; considerable flatus. Patient has consulted several surgeons, who advised operation for gallstones. We depend upon adrenal support to modify the adrenal cause of the asthenia and secretin with bile salts for the hepato-biliary difficulties and the constipation. The results were excellent.

TWO COMMON CASES

Here comes a widow with her two boys, Myron and William, aged eight and ten, respectively. The boys are rather pale and poorly nourished. They present enlarged lymph-nodes and tonsils. One of them has considerable adenoid tissue. The mother is timid about the thought of an operation. She asks if there is not something besides surgery that will prove of benefit to her boys. We take pleasure in prescribing a thymus-lymphatic gland formula, with the hope that an operation can be obviated in the one child at least.

A CRETIN

It is quitting time; but here comes another patient. We must spare time to see her. It is Ethel L., who was

one of my first patients on coming to the State some sixteen years ago. She is a cretin. When she came to me, her condition had not been recognized by any other physician. She was seventeen years old and almost an imbecile. She was 43½ inches tall, her girth at the umbilicus was 23¾ inches and around the chest, below the nipples, it was 22¼. She was of squat figure, her face was broad and putty-like in color. Her expression was stupid, her mouth hung open, she had very imperfect speech and answered questions slowly. She could scarcely walk across the room without being tired. All her bodily functions were slow. The bowels and kidneys were inactive, and heart action was feeble.

The treatment originally recommended at that time was thyroid extract, gr. V, t.i.d. The improvement was marvelous. After only one week's treatment, the patient ran away from home, and a neighbor found her a mile away. The girl became so lively and mischievous that her mother told me she didn't know whether she should continue with my treatment or not. Said she: "Ethel used to be such a good girl that if she died I knew she would go to heaven; but since taking your treatment she is getting so naughty that I don't know where she would go if she died." Ethel made progress mentally also. She learned to read and write. She grew nearly twelve inches in a year.

Ethel never became very strong. When she was a little more than twenty, her teeth began decaying. She was subject to myalgia and neuralgia. She caught cold easily. Her recuperative powers were below par. On this account, we are endeavoring to "remineralize" her system and she is also receiving half a grain of thyroid three times a day.

Well, let's shut up the office and chat for a while about these people. The cases seem to have been chosen somewhat at random; but it will be found that they are the usual cases met routinely by every general

practitioner. Let's see. We had cases of neurasthenia, eczema, asthma, epilepsy, nausea of pregnancy, morphinism, arteriosclerosis, lymphatism and hypothyroidism. What doctor has not met similar cases in his own practice? There is nothing unusual or startling about them. However, it must be admitted that these are among the most difficult cases encountered by the general practitioner. They present many occasions for stumbling. All of these cases previously had received other treatment at my hands and by other physicians; *but pluriglandular therapy proved to be the most successful means of dealing with these varied conditions.*

It may be contended that more simple medication in some of these cases would have proved equally successful. This contention seems scarcely logical in the light of these four facts:

1. The body is a complex mechanism. The state we call health consists of a multitude of delicate physiological adjustments. There is no anatomist or histologist or physiologist or psychologist of any repute who would not freely admit the complexity of the human body in health. Perhaps a single quotation at this point will answer our purpose. Henry Sewell (2) says: "It can hardly be doubted that the human organism responds to every kinetic energy acting upon it." We can scarcely forbear adding this also from Chapman's "Textbook on Physiology" (3): "When the vast complexity of structure exhibited by the human organization is considered, it becomes evident that any investigation of its function, however extended, if it be confined to man alone, can lead to but very limited results." In other words, the body contains many parts, many organs, many stystems—all bound together in a harmonious co-operating, co-ordinating entity. (4) Harmonious co-operation is the law of health. No better example of the co-operation given by the glands of the body can be found than that which takes place in a normal preg-

nancy. Some of the best-known signs of pregnancy are enlargement of the thyroid, liver, spleen, and mammary glands. (5), (6), (7).

2. If the body is complex in health, its pathological or disease processes cannot be other than complex. (7a) A delicate adjustment is disturbed and the whole organism suffers. The Apostle Paul (8) has put it very concisely: "And whether one member suffer, all the members suffer with it." The endocrine glands are, of course, no exception to this rule. A statement from *The Metabolist* (9) puts the matter clearly: "Owing to the reciprocal relationship that exists between these glands, a functional disorder of them is, in the last analysis, always a pluriglandular disturbance—never a monoglandular malady." Billings has also made a very similar statement: "Furthermore, it is universally recognized at present that the thyroid gland seems as one link of a chain of organs, and its aberration of function forms but a small fraction of the series of abnormal events occurring in all ductless glands." (10), (11), (12).

3. It is also true that our complex modern life makes for complexity of disease. When our forefathers were subduing the wilderness, there was little chance for a variety of occupational diseases. In the days of the log cabin, there was no lead colic; before the days of the aeroplane, there was no "aviation medicine." (13) Before the days of the bright lights, the days of exciting amusement and strenuous labor continued far into the hours normally dedicated to sleep, a neurotic patient was a rarity. At present, our occupations and our diversions give rise to diseases unheard-of by our grandsires.

4. If, then, disease is complex, is it not logical to infer that the treatment will often be far from simple? Curative medicine must meet a multitude of maladjustments. Modern therapy must assail these complex

diseases by applying all indicated measures *together*, even as the Allies *together* overwhelmed the Kaiser's resistance after the Yankees "got into the game." This is not only rational, it is clearly imperative.

Suppose that the automobile in which we have just visited these patients has been neglected. The water has gotten low in the radiator. As a result, the engine gets hot. The heat of the engine promotes combustion of oil. When the oil has reached the vanishing point, an engine bearing is burned out. Now comes a mechanic who tries to cure by the single remedy. Says he, "A depleted supply of water in the radiator has caused all your trouble. Let's fill the radiator and end your troubles." The radiator is filled, but the machine will scarcely run because of lack of oil and a burned-out bearing. Anybody has only to listen to the poor machine as it tries to limp along on three cylinders to know that the mechanic is wrong. "This will never do," you exclaim, "We must deal with effects as well as causes. Let's put in a new bearing, give her plenty of oil and water and then see how she works."

The point of my illustration is clear. The man who insists upon curing various endocrine disorders and the resulting ailments of the body with a single glandular extract is like the mechanic putting water in the radiator. He does not remedy the impairments that are present.

When will we medical men cease to follow cunningly devised theories to which we must make all the facts conform? Why not follow the facts, let them lead us where they will? Here is a series of cases of sufficient variety to prove to any open-minded critic that whatever formula was employed must have some merit. Our experience showed that we obtained results from the pluriglandular products that were not obtainable from other preparations used previously. Why not

acknowledge what is so palpably true instead of discrediting the testimony because it does not accord with the ideas of some?

Do we care so much for our pet theories that we are willing to sacrifice the best interests of the patient to them? If the patient is benefited by pluriglandular therapy, then why in the name of common sense should we not employ it? Call it "a reversion to the shotgun preparations of fifty years ago," (14) if you will. The point is not to find something with a pretty name, but rather, will this preparation do the work? We surmise that a sick man would not be particular whether the agent that effected his cure were named "orthodioxyphenylethanol-methylamine" (15) or some pluriglandular extract. The important question is, did he get better?

Some two thousand years ago there was a man whose sight had been restored by the Great Physician (16). The hair-splitters of that day insisted upon asking the method of the cure and what authority the man had for performing such a cure. They even questioned the evidence of their own senses when it conflicted with their preconceived theories. However, the thinking of this man, once blind, pierced through all carping criticism to the one essential, all-important fact. Said he, "One thing I know, that, whereas, I was blind, now I see."

Conditions have not changed so very much in 2000 years. Of course medical science has forged far ahead of its position in the first century; but for every patient who is cured today there is a group of eager faultfinders, who quibble about methods and names and theories and authority; forgetting that the main consideration is the cure of the patient. The truth is that this pluriglandular treatment is logical and rational and practical. It has cured patients for me. It will cure them also for you.

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VIII

THYROID THERAPY IN SOME INFECTIOUS DISEASES

By Dr. J. Koopman, The Hague, Holland

The possibilities of organotherapy in the treatment of infectious diseases have until quite recently been very poorly studied. This may astonish workers in the field of endocrinology; but none the less, it is quite comprehensible. In many other diseases where organotherapy has been tried, the control of the effect is often difficult or even impossible. Doctor, as well as patient, may suggest to themselves much that another perhaps would never be able to observe. I do not hesitate to assert that this is the reason why more nonsense has been written about the interesting and highly useful subject of organotherapy than any other medical topic. In the organotherapy of the infectious diseases, with which I shall deal in this paper (syphilis, typhoid fever), all phantasy and imagination is excluded and suggestion impossible, as the serological methods of examination give us a mathematical certainty of the correctness of our views.

In syphilis, the Wassermann test may be used as an indicator; in typhoid fever, the formation of agglutinins. Since two reactions belong, with many others, to the reactions on antibodies, I shall first try to give a general view of the influence of the thyroid on the formation of antibodies. The first opinion I found on this subject is formulated by Charrin (1), who stated that removal of the thyroid diminished the natural im-

munity of the animals against *B. pyocyaneus.* It is, however, well known that any operation may have the same influence in diminishing the natural resistance of the body. Sajous (2), Lorand (3), Müller (4, 5), Marbé (6, 7, 8, 9, 10, 11), and Palazzo (12), have found that the thyroid gland plays an important part in immunology and that removal of the thyroid in animals diminishes the opsonic index against microbes.

There are, however, many authors who do not confirm these views. Fassin (13, 14, 15), did not observe any difference in the amount of complement before and after thyroidectomy in animals. She stated, however, that experimental injections of thyroid extract or its oral ingestion in man increases the amount of complement. This last statement has been confirmed by Müller (5), Bianchi Mariotti (16), and Frouin (17); and Fjeldstad (18) never detected a difference between the formation of antibodies in animals with and without a thyroid gland. Frouin even goes further, for he states that animals from whom the thyroid is removed, give, when immunized against tetanus, a much higher antitoxic serum than the normal control animals. Very recently these experiments have been repeated by Garribaldi (19, 20). He found that in rabbits, which were injected with corpuscles of the sheep, the titration of the hemolytic antiserum was higher when the thyroid previously had been removed, than in normal animals. He also stated that the serum of thyroidectomized dogs had a higher amount of heterohemolysin than the serum of normal animals.

Stepanoff (21), has proved that the resistance of the body to infections is largely increased by the administration of thyroid extract. Parhon (22), was able to prove that thyroid preparations may prevent spontaneous infections in birds and other animals and that they even may play an important part in cholera prevention in men. Koopman (23), observed two rabbits

which did not produce an amboceptor of sufficient titer when injected with sheep corpuscles. In both animals the administration of thyroid was followed by a marked increase of hemolytic power.

These facts prove that not all authors agree upon the rôle of the endocrine organs in immunology, but many of them admit a highly important relation between the thyroid and the formation of antibodies. Still one other remark may be added: Gley (24), has introduced the word "tachyphylaxia" into physiology. This means that often after a first injection of an extract of an endocrine organ, that is followed by a marked physiological effect, a second injection has little or no effect at all. This so-called tachyphylaxis does not seem to exist in the influence of thyroid injections on immune bodies. In the experiments of Müller, a second injection of thyroid always gave a still larger increase of the amount of complement than the first one. Müller even found that when in an animal thyroidectomy was performed, injections of thyroid could produce a serum higher in complement than was even seen in normal animals when similarly injected.

But enough of these general remarks. This bibliography is by no means exhaustive; and it cannot be the aim of this paper to give a complete list of authors and titles. Those reading Italian and interested in this subject, may find much material in Barbara's book that may be warmly recommended. Let us now discuss the importance and clinical value of thyroid preparations in syphilis and typhoid fever.

THYROID EXTRACT IN SYPHILIS

The thyroid treatment of syphilis should have an enormous importance in medicine. All the same, its existence is hardly known to general practitioners, though this form of therapy is not at all new. Gordon (25), Eye Piece (26), and Menzies (27), saw splendid

results from this treatment. Spengler (28), has written a little book, in which he states that he has actually been able to cure dementia paralytica with mercury and thyroid. His monograph, however, contains so much nonsense, that the only thing that may be concluded from it is that his two "cured" patients did not have dementia paralytica at all. Nevertheless, one of Spengler's is perfectly right: There exists certain individuals with an increased sensitiveness to mercury; and many of these patients may take mercury without any trouble if thyroid is given at the same time. Perrin and Jeandelize (29, 30), have proved that thyroidectomized animals are intoxicated by much smaller quantities of mercury than normal ones. Wagner von Jauregg (31, 32), warmly recommends the combination of thyroid with other remedies in the treatment of syphilis. In one of his cases mercury had no influence; iodine did not agree with the patient. Then thyroid was tried. After some time iodine could be taken without trouble and the patient recovered. Some time later the patient died from an intercurrent disease; the postmortem examination was made and a very atrophical thyroid was found. Harrower (33), too, notes the importance of organotherapy in syphilis.

Though I have a great respect for clinical evidence, I have tried to control the influence of thyroid therapy in syphilis by laboratory methods—the Wassermann test. We may properly consider this test as a proof of methods to estimate the intensity of the reaction; but their value is limited. To prove this I should be obliged to write a monograph on the serodiagnosis of syphilis; so it must suffice for me to state that most authors are of the same opinion. Therefore, it is, in experimental work, better not to treat patients with a positive Wassermann test with thyroid and to study the effect of treatment on this reaction, for changes in the intensity of the reaction do not prove much. On the other hand,

patients with a primary induration are very satisfactory for this kind of work. When, however, in a suspicious ulcer spirochaeta pallida is found we have no right to wait with the abortive treatment till infection is generalized.

Now, I have treated five patients in whom no Spirochetes were found and where later the Wassermann test became positive and secondary symptoms developed, with the oral administration of thyroid extract (50 milligrams of the dried gland, 3 times daily). Of course there are other patients who have never developed secondary symptoms or a positive Wassermann treated in the same way. They are not mentioned here, as it never can be proved that they have been infected with syphilis. As a control, I have used six only locally-treated ulcers, which proved later on to be of syphilitic origin.

The Wassermann reaction is a modification of a test invented by Bordet & Gengou. This reaction of Bordet & Gengou is a real reaction between antigen and antibody. In the beginning, Wassermann and his co-operators believed that the syphilis test was based on the same principle. Though we cannot yet understand the physicochemical process of the Wassermann test, one thing is very probable:

This test is not a simple reaction between antigen and antibody, but rather is a test on a colloid-chemical change in the serum [Walker (35), Holker (35)]. The positive test may be considered as the first proof of the generalization of the pathological process. It is, however, of the highest importance to diagnose the syphilis before the Wassermann test is positive. Wassermann himself (37), has divided syphilis into two periods: a pre- and a post-Wassermann period. In the first period an abortive treatment is sufficient. In the second period, treatment may take many years. Was-

sermann states that this first period may be short; shorter than was believed in the time when the secondary syphilitic symptoms were considered as the first symptoms of a general infection.

During the last year a new reaction has been largely discussed, especially in German and Swiss literature—the reaction of Sachs-Georgi. I cannot take space to give any details here about this reaction. The general opinion is that in most cases this reaction parallels the Wasserman test. It may, however, be observed in the serum some time before the Wassermann test is positive, and would thus be a still earlier symptom of a generalization of the luetic infection. The short pre-Wassermann period is thus still too long, and the period in which abortive treatment is effective still shorter than Wassermann believed. The reaction of Sachs-Georgi has not been used in my experiments, as it was not invented at the time I was doing this work.

The first question we have to ask is: How long is this pre-Wassermann period? The literature on this subject is enormous.

Boas (32), gives this table:

No. of weeks after infection	Total cases
4	8
5	4
6	3
7	5
8	10
9	5
12	1

Bruck and Stern (39), state that in rare cases the Wassermann test may be positive before the primary induration is observed. In the already quoted report of the Special Committee upon the standardization of pathological methods (34), I found one case where ten days after infection the Wassermann test was found positive by three different workers. Craig (40), ob-

served a positive reaction in 36.3 per cent of 600 cases during the first week. He gives his table:

Weeks after appearance of chancre	Total cases
1	77
2	155
3	158
4	167
5	43

The tables of Boas and Craig cannot be compared with each other as the first one counts from the moment of infection; Craig, however, from the appearance of an ulcer. We have seen that in some cases the Wassermann test may even be positive before a chancre may be observed. Citron (41), considers 57 days after the infection the average time for generalization of the syphilitic infection. As I said in the beginning, my own material was very small. I observed 6 cases with ulcers in which I could not detect the Spirocheta pallida, and who developed later secondary symptoms and a positive Wassermann test. Three cases became positive four weeks after infection; one case five weeks; one case seven weeks and one case eight weeks. Other cases are not quoted here, as I stopped examining when 13 weeks after infection the reaction was still negative.

Now, in a number of cases with ulcers, thyroid was given by mouth, 3x50 milligrams of dried gland daily. My idea was this: When the reaction of Wassermann is a sign of generalization of the infection it must be possible to delay this moment by increasing the resistance of the body. Now, the previously quoted authors have found that ingestion of thyroid increases this resistance as is shown by the increase in the opsonic index of the blood. Unfortunately, it is practically impossible to estimate this index against the *Spirocheta pallida* at least when one is not working in a good bacteriological laboratory, as the handling and pure culture of *Spirocheta pallida* is less easy than might be

concluded from many text books. But though it is difficult to give a mathematical way of measuring the resistance of the body to a general invasion by the Spirocheta, the time elapsing between the local and general infections permits us to have an idea of this resistance.

That the thyroid plays a most important rôle in defending the organism against an invasion may also be proved by clinical symptoms. Nearly all authors describe as the first clinical symptoms of secondary syphilis, skin eruptions; but these may be accompanied or even preceded by marked symptoms of a disturbed function of the thyroid gland. This was first described by Engel-Reimers (42), who found very frequently, especially in syphilitic women, all symptoms of what he called, "thyroidism." Mauriac (43), has even described a *"goitre aigu syphilitique secondaire."* Delpy (44), agrees with Engel Reimers, though, according to him, the eruption often is observed some time before the symptoms of thyroidism. As I am writing neither an essay on syphilis nor a study on dysthyroidism, I shall not try to describe the symptoms of dysthyroidism, which may be found in most modern books, for instance, in the quoted book of Harrower (33), or in a very exhaustive way in the book of Chvostek (45).

At last I come to my own small number of experiments. I found that in four of the five patients who took thyroid during the period between the moment of infection and the beginning of serological changes was much longer than in the control patients. In the first case treated in this way, the Wassermann test became positive 12 weeks after the infection. In three other cases it took 10 weeks; in the fifth case 7 weeks. Now, I am quite aware that these few cases are not enough to prove anything with certainty, but they give us a right to continue our studies in this direction. Obviously, it is of the greatest importance to make the period

as long as possible to prevent the patient from the dangers of general syphilis. Two things are absolutely sure: 1. The thyroid gland plays a prominent part in syphilis; 2. Thyroid therapy has a future in treament of syphilis.

EXPERIENCES WITH TYPHOID FEVER

It is a fact that the thyroid is sometimes affected by typhoid infection, but this fact is not at all generally known. In many of our well-known textbooks I found nothing on this subject. Dieulafoy (46), mentions suppuration of the thyroid as one of the complications of typhoid fever. Gilbert and Castaigne (47), report a remarkable case where a typhoid fever was the cause of, or at least followed by, a Graves' disease.

Out of 1700 cases of typhoid fever Liebermeister and Hoffmann (48), found 15 cases of thyroiditis and strumitis. An interesting case is published by Geza Galli (49), where a patient, 21 years after a typhoid fever, developed an abscess in the thyroid. After incision, the pus proved to contain a pure culture of typhoid bacilli. Roger and Garner (50), found in typhoid fever anatomical lesions in the thyroid. In several serious cases they observed a hemorrhagic inflammation of the organ. Crisafi (51), found anatomical changes, but was not able to isolate the typhoid bacilli from the thyroid. Pernice (52), described typical lesions in the thyroid: hyperemia and a hypersecretion of colloid.

Now, though we know the influence of typhoid bacilli on the thyroid, we must not exaggerate the meaning of this. Nicholson (53), thought that endemic goitre was caused by an infection due to a water-borne organism. He supposed that this, perhaps, could be the typhoid bacillus. So he treated his patients with goitre with inoculations of typhus vaccine, without success. This result will not astonish most workers.

We have been speaking heretofore of the anatomical changes caused by typhoid bacilli. We shall try now to discuss the influence of thyroid preparations upon the serological processes that take place in the body. Here we may expect to find out additional facts, as the case of syphilis. Syphilis, at first, is a local infection which later becomes general. Typhoid fever, on the other hand, is a general infection, as is proved by the findings of bacilli in the blood during the first few days, which later becomes localized. There exist even (extremely rare) cases of sepsis by typhoid bacilli without localization (Bonn, 54). The organism defends itself through the production of agglutinins, and these may be detected in the blood from the second week of the diseases. There is not much literature about the influence of thyroid administration on the formation of agglutinins. Fjeldstead (18), immunized rabbits against typhoid bacilli and did not find any difference between normal animals and animals after extirpation of the thyroid. Borchardt (55), found that most endocrine organs (pituitary, adrenals, thyroid) raise the agglutinin titer in a very marked way.

My own experiments give results similar to Borchardt. The first experiment was performed on two guinea pigs (with two others serving as a control). The first guinea pig was injected with a small quantity of living typhoid bacilli (10 millions). The strain was very pathogenic, as the animal died in 18 hours (at post mortem I found all the symptoms of an acute sepsis). The control animal received the same dose of bacilli and also 10 milligrams of an extract of thyroid. This last one is still alive and never did develop any symptom of disease.

Another experiment had the same result. One guinea pig got 5,000,000 typhoid bacilli; the other the same quantity and 10 milligrams of thyroid extract. This strain did not seem to be so virulent. The first

animal was ill, it did not eat for two days, it sat quietly in a corner of its cage, whilst on the other hand, the second animal did not show any symptom at all.

Then I did some clinical work on patients. In all cases where typhoid infection was a possibility I examined the blood for bacilli. Nearly always this was negative, and the patient did not get typhoid fever. In three cases it was positive and in these cases immediately thyroid was given by mouth. I will very briefly report these cases here:

1. A boy of 17. Complains of headache, thirst and dullness during some days; spleen not palpable; no bronchitis; no temperature between 38.4° and 40.2°; pulse, 74, dicrotic; the blood culture showed typhoid bacilli. Agglutination on the fifth day of the disease, 1:25. Then 40 milligram thyroid was given 3 times daily. On the sixth day the agglutination is 1:200; on the seventh, 1:250; on the 8th, 1:2000. After that it did not rise any more.

2. Man of 22. Same complaints as No. 1. Spleen not palpable; there is bronchitis; no rose spots; temperature goes to 40°; pulse, 90, dicrotic; typhoid bacilli were found in the blood. Agglutination on the fourth day of the disease, 1:10 thyroid was given 3 times daily. Forty milligram agglutination on the fifth day, 1:200; sixth day, 1:1500; 8th day, 1:2500. This last was the maximum figure.

3. Man of 24, with tuberculosis of the lungs and tubercle bacilli in sputum; was under observation during some time when one day temperature rose to 39.4°. Some days, before the patient had been dull, the blood contained typhoid bacilli. There was no agglutination. Thyroid was given from the third day; fourth day, titer 1:100; fifth day, 1:300. Sixth day the patient had a collapse and died suddenly. We see here in three cases how by the influence of thyroid therapy the formation of antibodies begins much earlier than in other cases.

For this to be accomplished, it is necessary that a diagnosis be made as soon as possible.

In five cases of typhoid fever, where no bacilli were found in the blood and where the Widal-reaction was already positive when I began with thyroid tablets, I have not seen the slightest influence on the measure of agglutination. In the same way I did not observe a difference in agglutination after vaccination against typhoid fever in persons taking or not taking thyroid tablets. It is difficult, even often impossible, to diagnose typhoid in the beginning of the disease. If, however, the diagnosis is made early, we ought to think of the possibility of increasing the resistance of the patient by giving him thyroid. Perhaps other endocrine products may have the same or an even better effect, but one thing is certain: Too often the endocrine system is forgotten in the study and the treatment of acute infectious diseases.

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IX

THE THYROID-OVARIAN SYNDROME

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Endocrinology at the present time is still a rather confused subject. Marked and typical cases of endocrine dysfunction are recognized without difficulty, but the so-called *"formes frutes"* of these same disturbances are all too seldom diagnosed. The importance of the endocrine system in everyday medicine is being more and more emphasized by the discovery of new syndromes. As each new syndrome is recognized and described, the present confusion is becoming less evident. All of the syndromes have symptoms explainable on a basis of disturbed physiology, and once the exact modus of this disturbance is understood, organotherapy becomes more rational, and hence more successful.

The basis of success in endocrine therapy rests on the fact that no one gland is ever individually diseased, in the sense that it may be the sole cause of all of the symptoms present. The glands of internal secretion form a closely-interrelated system and what affects one affects all, though in different degree and manner. Treatment, therefore, in order to be successful, must be based upon a consideration not alone of the gland obviously diseased, but also of those indirectly affected. Lack of observation of this important principle is the most frequent cause of failure in therapy.

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The thyroid gland is concerned chiefly with catabolic metabolism, hyperfunction resulting in rapid loss of weight, hypofunction in adiposity. In addition to changes in metabolic activity, dysfunction is also manifested by various nervous symptoms, hyperfunction by excessive nervous irritability, hypofunction by mental sluggishness. The functions of the ovary are by no means as clearly manifested. One obvious function of that organ is the production of ova, and another much less understood function is that of the control of the secondary sexual characteristics. This function is to some extent controlled by the interstitial chromatophilic cells and these probably are similar in character to the interstitial cells of Leydig found in the testes.

The thyroid-ovarian syndrome is a *"forme fruste"* of dysfunction either of one gland individually, or of both glands concurrently. Isolated phases of the syndrome have been described as clinical entities, but as far as a thorough search of the literature reveals, no one has grouped the various symptoms as a distinctive syndrome.

Strangely enough, the syndrome may occur in either male or female, though the female was affected in forty-one of the forty-five cases which we have thus far observed. In the male, testicular dysfunction replaces dysovarism. The onset of symptoms may be at any period after the beginning of puberty, the age incidence in the present series being twenty to thirty years, five cases; thirty to forty years, sixteen cases; forty to fifty years, twenty cases; fifty to seventy years, four cases. No etiological factor other than the possible influence of heredity is in evidence. Sister, or sister and brother, were affected in twenty instances, while in eight other cases near blood relatives, *i. e.*, mother, were said to be similarly diseased, though these eight have not been personally examined.

In the early stages the symptoms may be referred either to the ovary or the thyroid; in well-marked cases both glands are equally involved; and in late cases symptoms of thyroid dysfunction are the more prominent. The syndrome is for the most part one of hypofunction, though some cases show marked evidences of hyperfunction of one of the glands—this probably as a manifestation of what might be termed a terminal compensatory effort.

BACKACHE A COMMON SYMPTOM

The sequence of symptom development varies with the type of case. Where the ovary initiates the condition (twenty-two of forty-one cases), the first complaint was a pain in the back just above the sacrum. This pain could not be explained by any static condition, such as flat feet, etc., neither was it relieved by treatment directed to the correction of a static condition. A characteristic of the backache is that it is relieved during active menstruation. In a few cases the control of a coincident constipation also afforded marked relief. The pain often radiates down one or both legs, at times to the knee, either along the course of the sciatic, or genitocrural nerve. In two cases a laparotomy was performed, because of this symptom, and what were said to be systic ovaries were removed. The backache was not influenced by this procedure.

Accompanying the backache there may or may not be menstrual disturbances, either amenorrhea, or a brief period of profuse menstrution, followed by amenorrhea. Later, there may or may not appear varying degrees of hirsuties. In one case the patient was very definite in asserting that the growth of hair was most marked one week before menstruation. Physical examination shows no characteristic pelvic condition other than extremely sensitive ovaries, and even this is not constant. The ovarian type is found in those

in whom sexual life is still active, and represents the condition known as hypo-ovarism. It may last for from two to five years before merging into the fully developed syndrome.

As illustrative of the condition, the histories of three cases are briefly cited:

Case I. A married female, 38 years of age, with a negative past and family history, and who had had three normal children after uneventful labors, presented herself with the complaint of severe backache and weakness. She had previously been treated for flat feet, varicose veins, relaxed abdomen, a relaxed sacroiliac joint, an arthritis and a supposedly relaxed perineal floor—all without result. The onset of symptoms dated back three years, and was gradual. At first, the backache was intermittent; later, continuous and typical. Menstruation at the onset of the backache had been freer than usual, latterly it was scanty and the periods were irregular and from two to three weeks late. Her weakness dated back four months, and could not be attributed to any intercurrent infection.

It may be said here that in all the cases reported here the physical examination included a complete serological, cytological, and chemical examination of the blood, a complete examination of the urine and feces, and an exhaustive physical examination, including the organs of special senses and the nervous system. Physical and laboratory examinations were negative except as stated below.

The patient was 15 pounds overweight; there were slight hirsuties on the chin; the abdomen was pendulous and supported by a belt; there were slight superficial varicosities on the lower legs; and the perineal floor was relaxed. The pelvic organs showed no other demonstrable lesion.

Case II. An unmarried female, 29 years of age. Chief complaint, pain in the back, radiating down the thighs to the inner aspect of the knee. Pain absent during menstruation and markedly relieved by permitting herself to remain constipated for three days. These pains had commenced at her nineteenth year and, at times, were so violent as to incapacitate her for work. When she was twenty-seven years old both ovaries were removed (diagnosis: chronic oöphoritis, cystic ovaries). There had been no relief of the pain except for two months directly after operation. At present, she also complains slightly of the usual symptoms associated with the surgical menopause.

Physical examination: Five pounds overweight, all reflexes extremely active, properly corrected error in ocular accommodation, pelvis negative except for extremely sensitive areas in both lateral fornices.

While therapeusis will be considered later it may be noted here that the pain was relieved by organotherapy.

Case III. Married female, aged 42 years. For the past eight years she has suffered from a backache and what has been diagnosed as a chronic sciatica of the left leg. No treatment which had been applied relieved the pain in the back. The pain in the leg is intermittent and is always relieved at the establishment of menstruation. Menses normal up to two years ago; since then, irregular (over time) and profuse. She has four children alive and well.

Physical examination: Overweight 28 pounds, marked hirsuties on lip and chin; mitral endocarditis; blood pressure 160 mm. systolic, 110 diastolic; abdomen pendulous; lacerated cervix and perineum, the latter supported by a properly-fitting pessary; slight varicosities of right leg; moderate degree flat feet, supported by properly fitted arches; mild secondary

anemia. Laboratory examinations: Urine faint tracé of albumen. Sp.gr. 1010 to 1014, few hyaline casts.

CASES WITH INITIAL DYSTHYROIDISM

The cases which commence with thyroid disturbances first complain of a series of symptoms similar to those usually associated with chronic nephritis. Frequently the first symptom is a headache, which comes on early in the morning, often awakening the patient from sleep and lasting until midday. Dizziness and double vision are also frequent occurrences. If the blood pressure be taken at this period it will be found to be increased, in some cases alarmingly so, 200 mm. of mercury being not infrequent. This increase in blood pressure in women at the menopause has been commented upon by others. A gradual development of trophic or metabolic disturbances follows. There is frequent complaint of itching. The hands are described as feeling boggy and stiff in the morning, finger rings being turned around with difficulty then, and without difficulty later in the day. There is a slight edema of the legs and the skin feels puffy.

Physical examination shows little or no change from the normal. Occasionally the second aortic heart sound is accentuated. Laboratory examinations for kidney involvement are negative. Occasionally there are mild or severe evidences of hyperfunction (4 of 16 cases) with nervous irritability, and in one case glycosuria. In two cases a temperature varying from 99.4° to 100.8° F. *(per os)* persisted for eighteen months to two years without demonstrable cause.

The onset of these symptoms is rather acute and they last with varying severity from two to seven or eight years. The skin during this period gradually becomes drier; there is a marked gain in weight, averaging in twenty-seven cases, 35 lbs.; the hair becomes brittle. The types commencing as thyroid dysfunction usually

occur in those either at, or past, the menopause and are the type encountered in the male. In this group the thyroid symptoms persist for a longer period before the development of the complete syndrome than do those in whom the ovarian symptoms are the initial ones.

Four cases showing various phases of the thyroid type are detailed in the following paragraphs:

Case I. Married female, aged 56 years, mother of eight children, all alive and well. Past and family history negative except that two sisters, both older than the patient, are suffering from similar symptoms. For the past three years the patient has suffered from headaches which occur in the early morning, usually awakening the patient about 4 A.M. These headaches are sometimes frontal, and other times occipital, and usually disappear about midday. She has had many attacks of vertigo, sometimes so severe as to cause her to fall over and associated with vomiting when severe. In the morning her feet are slightly swollen and during the day there are transient attacks of swelling of the lip. Her hands feel swollen and at times her wedding ring can be turned only with great difficulty. She has gained 46 lbs. in six years, though she describes herself as "a very small eater."

Physical examination shows a slight ocular error, which is properly corrected. There is a slight enlargement of the heart to the left, with an accentuation of the second aortic sound. The blood pressure is 210 mm. systolic and 100 diastolic. The abdomen is relaxed, but otherwise negative, and the pelvis is normal except for a lacerated cervix and perineum. She is 51 lbs. overweight, and the skin is dry and feels boggy.

Laboratory examinations: Urine, 2100 c.c. in 24 hours, sp.gr., from 1008 to 1025; Mosenthal diet as a kidney function test shows no evidence of salt or nitro-

gen retention; blood chemistry, serology and cytology negative; phenosulphonepthalein output normal.

Case II. Male, 56 years of age, married, no children. Chief complaint, violent headaches coming on about 5 A. M., lasting until about 2 P. M.; marked weakness and attacks of vertigo of intermittent character. Duration of symptoms, 9 months. At present almost bedridden, because of weakness and uncertainty in gait.

Physical examination shows that he is 20 lbs. overweight. His blood pressure is 190 mm. systolic, and 90 diastolic. Heart action is forcible, but there is no enlargement. There is no ocular error, and thermic tests of the semicircular canals show no abnormality. The skin is rather syanotic and dry, and the hair is brittle.

Laboratory examinations: Urine, 1700 c.c. in 24 hours; sp.gr., from 1015 to 1022; there is a faint trace of albumen and an occasional cast. Chemical examination of the blood, Mosenthal test diet, and phenolsulphonepthalein test all fail to show evidence of kidney involvement. There is a mild secondary anemia.

Case III. Male, aged 47 years, married, 3 children, alive and well. Chief complaint, vertigo, swelling of the lower limbs in the morning, itching of the skin at night. Duration of symptoms, eight months.

Physical examination: 18 lbs. overweight (this extra weight has been gained in the past year); reflexes very active; blood pressure, 185 systolic; eyes and ears normal. The heart is slightly enlarged, and there is a faint murmur at the aortic valve transmitted up into the vessels of the neck. There are numerous scratch marks and areas of pigmentation on the legs.

Laboratory examination: Urine, 1900 c.c. in 24 hours; sp.gr., varies from 1013 to 1030. Sugar present in amounts varying from one half to two and a half per cent., no acetone bodies. Blood chemistry and Mosenthal test diet, as well as phenosulphonephthalein test,

negative for evidences of nephritis. Blood sugar 125 mgm. per 100 c.c.

Allen treatment for glycosuria cleared up the urine; the blood sugar values remained practically unchanged, ranging about 115 mgm. This treatment gave no relief of either symptom. Organotherapy relieved all symptoms in approximately fifteen days and, while on organotherapy and a diet especially rich in carbohydrates, he showed no glycosuria.

Case IV. Female, single, aged 34 years. Chief complaint: Weakness, violent headaches in the morning, chiefly occipital; dizziness; edema of the hands and a continuous fever for a period of eighteen months, ranging from 99.2 to 100.6 degrees *per os*. The patient is a trained nurse, and she has gained weight in spite of symptoms.

Physical examination: Negative, except for a pulse of 100 to 105 without a cardiac lesion. Overweight, 25 lbs. There is no ascertainable cause for the temperature, complete radiographic examination of all possible foci in head, chest, and abdomen being negative. Blood pressure, 145 mm. systolic.

Laboratory examination: Urine, 1450 c.c. in 24 hours; sp.gr., from 1010 to 1015; faint trace of albumen and an occasional cast. No evidence of nephritis upon special examinations.

THE TWO SYNDROMES

There are then two distinct pictures, one referable to the ovary and similar or identical with the condition commonly recognized as hypo-ovarism, which lasts for from two to five years; and the other referable to the thyroid. The latter presents the symptoms usually associated with a chronic nephritis and lasts for from two to eight years. The ovarian type occurs only in the sexually active female, the thyroid type may occur in the sexually active female, but is more likely to develop

after the menopause and is the type seen in the male. With the progress of the condition, irrespective as to which gland is first involved, the terminal condition presents a predominance of the thyroid symptoms. As illustrative of the terminal condition, two cases, one male the other female, are cited.

Case I. Female, married, age 38 years. One child died of intestinal obstruction, three others are alive and well. During the last pregnancy, four years previous, she complained of headache, vertigo and a slight and transient edema of the legs. At that time her blood pressure, which one year previous had been normal, was found to be 180 mm. systolic and a trace of albumen and casts were found in the urine. The diagnosis of impending eclampsia was made and she was placed in the hospital under close observation. The complaint of headache became so intense at the middle of the eighth month that a premature labor was induced. After delivery the headaches became less severe, the vertigo intermittent and more severe, periods of double vision occurred, and the blood pressure and urinary findings remained as before delivery. A diagnosis of chronic nephritis was made.

The conditions remained as just described for a period of two years when an intolerable itching developed which kept the patient awake at night. The skin became boggy to such a degree that larger shoes had to be worn, and rings had to be removed from the fingers. There was an increase of 49 lbs. in weight. Attacks of double vision became increasingly more frequent and lasted longer. A backache developed about six months ago.

After the birth of the last child there was a period of six months during which menstruation, while regular, was very profuse, but latterly it had become irregular—being sometimes four to six weeks overdue—and when on time, it was scanty, being approximately one-

third that previously experienced when in health. The patient, a trained nurse and the wife of a physician, was very morose and downcast at the prospect which confronted her.

Physical examination showed a large-framed female 55 lbs. overweight, with a dry, scaly skin, which was decidedly boggy. Her blood pressure varied between 175 and 200 systolic. The cardiac area was enlarged a trifle to the left. There were scratch marks on the legs and back.

Laboratory examination: No evidence of nephritis in the results of blood chemical examination, a Mosenthal test diet, or a phenolsulphonephthalein test. A slight secondary anemia was present. No pathological condition of the pelvic organs other than a slight laceration.

While the therapeusis of the condition will be considered later, the subsequent course of this case makes it necessary to refer to medication. She received ovarian gland substance, 15 gr., and thyroid gland, 3 gr., three times a day for a period of ten days. At the end of that time she reported that the headaches and double vision had gone and that she had lost eight pounds in weight. Her blood pressure was 165 mm. systolic. This medication was continued for a period of two months, during which period she was symptom-free, having neither itching, double vision, headaches, nor backache. The loss of weight was 35 lbs., blood pressure 145 systolic. The dosage of thyroid was reduced to one half grain and that of ovarian substance to three grains. After three weeks of this treatment she reported that she had felt perfectly well up to ten days before her menstruation, when double vision had returned rather severely for two days. The ovarian substance was increased to ten grains and the thyroid to one and a half grains. This was continued for two months, during which time she was symptom-free and

lost an additional ten pounds. It might be noted that while she had been on a restricted diet for several years, during organotherapy she was placed on a full diet. Thyroid alone in one-half-grain doses was given for the next two months, with the result that she did not menstruate the second month and again ten days before her period had double vision for five days. The medication was reinstated as before, for one month, the double vision cleared up and did not return at the next menstrual epoch. Between two menstrual epochs she was given pituitary gland substance, and after four days of medication, double vision recurred worse than ever before. It subsided promptly when pituitary substance was discontinued. At the present time her status is that of a well woman—blood pressure 125 systolic, symptom-free, urine normal, menses normal, total loss of weight 55 lbs.

Case II. Male, age 56 years, married, four children, all alive and well; negative family history except that he is the brother of Case IV, thyroid group. About seven years ago the patient noted a gradual increase in weight and the onset of attacks of vertigo and shortness of breath, this last being attributed to his gain in weight. Five years ago, though previously free from headaches, he commenced to have violent morning headaches, which aroused him from sleep at about 5 A. M. These headaches were frontal and temporal, and wore off during the day. He had occasional itching of the skin at times violent enough to prevent him from sleeping. He had a nocturnal polyuria. Latterly, he had frequent periods during which he could not read the paper because of double vision. Six months before the present period he had been rejected for life insurance because of high blood pressure. Within the past year he noted a sudden dimunition in sexual power.

Physical examination: Overweight, 30 lbs.; blood pressure, 250 mm. systolic; face "puggy" and cyanosed;

legs edematous up to the knee; hands edematous; heart enlarged to the left, no murmurs; abdomen large and pendulous; skin dry; eyes and ears negative.

Laboratory examination: No evidence of nephritis by special examination. Urine, 1975 c.c. in 24 hours; sp.gr., 1020 to 1023, trace of albumen and moderate number of hyalin and granular casts.

Subsequent course under organotherapy of 3 grains of thyroid and 5 grains of ovarian substance (ovarian gland was given because commercial testicular extracts have, in our experience, not been effective), and later reductions in the thyroid dosage showed at the end of six months a loss of 38 lbs. in wight. Blood pressure, 147 mm. systolic; edema, itching and headaches, as well as double vision, gone. A course of four grains of pituitary gland substance three times daily for four days brought a prompt return of the double vision.

DIAGNOSTIC CONSIDERATIONS

The differential diagnosis of the ovarian complex is not difficult. Static conditions, such as flat feet, lacerated perineum, etc., must be eliminated as a cause of backache, and the general complaint of weakness must not be attributed to neurasthenia, whatever that term may mean.

A carefully-taken history is essential and a careful search for evidence of loss of secondary sexual characteristics, i. e., development of hirsuties, is essential. The thyroid group present a difficulty in diagnosis, in that the condition of chronic nephritis is very closely simulated. This difficulty may be eliminated either by the special tests which have been mentioned, i. e., the Mosenthal test and blood chemistry, or they may be eliminated by therapeutic tests, i. e., treating the case as if it were an endocrine deficiency, and if no improvement occurs changing the diagnosis to a chronic nephritis.

As has been stated before, the key to successful organotherapy is a consideration and understanding of physiology. The initial symptom of the ovarian type, namely, backache, is possibly of purely mechanical origin. The relief at the menstrual epoch makes it seem probable that the pain is brought about by pressure from within the organ which stretches the capsule. The radiation of the pain is explainable by the innervation, nevertheless, the persistence of pain after oöphorectomy is against such an explanation.

The first symptom referable to dysfunction is a partial loss of secondary sexual characteristics. The loss of function as applied to the menstrual cycle is the last to appear. Occasionally the organism makes a violent attempt to keep up its function and this is clinically manifested by a profuse menstruation. Finally the menstrual stimulation becomes less and less and amenorrhea is the clinical manifestation. The ovary is in intimate connection with the thyroid, a fact well known to all. The pituitary relationship is just as evident, for activity of the ovary (pregnancy) frequently is accompanied by an almost adenomatous proliferation of the pituitary.

The thyroid behaves in a manner somewhat analogous to the ovary. The first insufficiency is one of decreased catabolic metabolism indicated by increase in weight. As with the ovary, occasionally the gland, in a final effort at compenstaion, works overtime and nervous irritability, glycosuria, or temperature changes may be the clinical result, just as these symptoms so often are seen in atypical cases of Graves' disease. It is probable, but not proved, that the normal thyroid to some degree inhibits pituitary activity. When this inhibition is removed, i. e., when there is thyroid dysfunction, there is hyperpituitarism indicated by high blood pressure and headache. This is the reverse of the ovarian type where hypopituitarism occurs as is

indicated by weakness and often low blood pressure. The headache is probably caused by an enlargement of the pituitary and this same enlargement possibly also causes a partial and temporary paresis of the ocular motor muscle by pressure upon the nerves. Further evidences of disturbed catabolism are shown by the myxedematous condition of the skin, the transitory edemas, and the itching.

Irrespective as to which link in the chain breaks first, eventually all are involved, and the pluriglandular symptom complex results. A close observation particularly of so-called chronic nephritis will reveal a surprisingly large number of individuals who have this condition.

PRACTICAL THERAPEUTIC DEDUCTIONS

The therapy of the condition based upon the altered physiology is relatively simple. When the evidence points to an initial ovarian insufficiency, large doses (15 grains) of the ovarian gland substance, with small doses of pituitary gland substance (1 to 2 grains), are to be tried first. If there is not relief then small doses of thyroid gland are added (one-half grain). The medication is given three times daily. In those cases commencing with thyroid disturbances relatively large doses of thyroid substance (2 to 3 grains), and smaller doses of ovarian substance (5 grains) are administered. In the latter type pituitary gland is contraindicated. In the terminal well-developed syndrome a large thyroid and small ovarian medication is the proper one. The intensive medication should be kept up until there is either relief of symptoms or toxic manifestation. It has been our experience that ovarian cases must be kept under intensive medication for approximately four weeks before there is relief, while the thyroid cases show improvement in approximately two weeks. When there is almost complete relief of symptoms the dosage

should be reduced one half, but it must be kept up constantly for a period of from three to six months in order to have the relief continuous. After the six months' period medication may be reduced to approximately one quarter of the intensive dose, and it need only be given intermittently, say, for two to three days in the week—this, however, must be continued either indefinitely or for very long periods.

It goes without saying that the treatment outlined is not a matter of rule of thumb, judgment must be used particularly in the administration of the thyroid. A rise in the pulse rate, the rapid loss of weight, diarrhea and the development of nervousness are all indications of toxemia and indicate the need for less intensive dosage. When the normal weight has been established it is well to allow a further reduction of five pounds and then endeavor to hold it at that figure. While occasionally the administration of a single gland may prove to be effectual, such cases are, in the experience of everyone, relatively rare. Success is much more uniform when the various glands are combined according to the scheme indicated. The criticism may be made that a so-called "shotgun" therapy is advocated, however, it is "shotgun" therapy only to those who do not understand the altered physiology upon which it is based.

In the body of the article we have purposely refrained from discussing the work of others who have considered one or another phase of the syndrome. For those who may be interested, the recent literature pertaining to the subject in its various phases is appended.

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X

DYSTHYROIDISM: THE RATIONALE OF ITS TREATMENT

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An explanation of the notoriously unsatisfactory therapeutic results obtained in hypersecretory conditions of the thyroid is to be found in the general truth that rational and effective therapy must be based upon exact knowledge of the etiologic factors which produce the pathologic state. Lack of this certain knowledge of thyroid pathology accounts for the indefinite state in which the therapy of this disease exists.

The nomenclature used in the extensive literature of this subject reflects this uncertainty. Hyperthyroidism, thyrotoxicosis, dysthyroidism, dyscrasia, toxic adenoma, exophthalmic goitre, toxic goitre and other terms are used by different authors to describe the same or very similar clinical pictures. All of these terms have in common the endeavor to express a disturbance of function, an abnormal physiologic state, and this is, in truth, as far as it is safe to go. The term "dysthyroidism" best describes the condition and its use has the advantage that it does not commit one to any particular theory, especially since an open-minded attitude would seem to be the best to assume in the light of our present information.

The basic factor necessary for a better understanding of thyroid pathology is a thorough knowledge of

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* *The writer of this essay received the fifth prize of $25.00.*

thyroid physiology. This we do not possess. Great strides have been made in this direction. Thyroxin recently has been isolated by Kendall, but the functions of this active principle, other than that it is a stimulator of metabolism, are yet to be revealed. The probable existence of other hormones is not disproven nor does the discovery of thyroxin throw much light on the pathologic physiology of the thyroid. McCaskey[1] has interpreted this discovery as firmly establishing the theory of hyper- and hypo-secretory types of the thyroid functioning, and leaving "no chance for a claim of dysthyroidism." He fails, however, to explain satisfactorily the presence of some of the symptoms of so-called exophthalmic goitre in a cretin.

Other undeniable clinical facts, which are contradictory in the theory of hyperthyroidism, fit in quite well with a theory of dysthyroidism which Janney[2] has very ably advanced and in favor of which has adduced much evidence. Sclerodermia,[3] keratoconus,[4] episcleritis, and localized trophic disturbances, especially of the eye, which are benefited or cured by thyroid extract, support the theory of dysfunction, especially when they occur in cases of both hyper- and hypothyroidism, so-called.

The little knowledge which we possess concerning the causes of dysthyroidism has elucidated the problems only slightly. Nervous shock, infections, puberty and the menopause are only indirect causes and do not in all individuals produce thyroid dysfunction. The ultimate, direct cause is still to be ascertained. Who shall discover it, the physiologist, the pathologist, the surgeon or the clinician?

Most of our information regarding thyroid conditions has been obtained by surgeons, and the whole subject is viewed very largely from a surgical aspect. The habit of resorting to surgical measures as soon as the diagnosis is made has become so widespread that the

laity have come to believe that it is a purely surgical condition. This attitude has arisen through the fact that apparently better and quicker results are obtained by partial thyroidectomy than by medical measures. In the great majority of cases the latter have not been given a thorough trial, consequently results in these have been attended by failure, which always follows insufficient and half-hearted treatment.

One might question the advisability of considering other means when surgery seems to offer quick relief from symptoms and ultimate cure. Without at this time entering into a discussion as to whether or not surgery really accomplishes this result, let us consider another aspect of the problem. Granting that good results are obtained by operative means, it does not necessarily follow that surgical treatment is the most rational or productive of the greatest ultimate good. The logic of surgical treatment as applied to dysthyroidism is subject to some criticism. Whatever theory is adopted as to its etiology or whatever term is used in describing it, the pathologic state in every case is one of perverted function. Removal of a gland or part of a gland is hardly justified because it is not functioning properly. Surgery is not resorted to in any other instances of pure dysfunction of an organ. The unquestioned fields of surgery are removal of malignancies, removal and drainage of infected tissues, correction of skeletal defects and repair of soft tissues. It is not the usual procedure to remove an organ for any other cause than malignancy or infection which is so advanced as to make the organ's retention in the body a menace.

The application of surgery to thyroid disturbances came about through the conception of this condition as one of hyperfunction and the attempt was made to remove a large portion of the gland, leaving just enough to supply body requirements.

The immediate results afford some relief to the patient, but it is difficult to say exactly how much it is necessary to remove in order to restore normal function. When symptoms do not abate, a second operation with removal of more thyroid tissue is frequently resorted to. (Sloan,[5] Beebe[6]). The other extreme, operative myxedema, is an infrequent subsequent development at the present time.

Although improvement is the general rule following lobectomy, a complete and immediate cure is rarely the case. (Bram[7]). *Surgery does not remove the cause,* but rather the result of abnormal function. It is a difference in degree only between this operation and that of removing the superior cervical sympathetic ganglion (Mayo[8]) for the cure of exophthalmos, an occasional symptom of dysthyroidism.

Clinicians and surgeons both have come to recognize that dysthyroidism is a self-limited disease which runs its course and goes on to recovery (Stanton[9]). This being true, operative procedures merely modify the course and do not effect a cure.

Thyroidectomy in this instance is comparable to splenectomy in pernicious anemia. In the latter case a remission is frequently produced, but the general course of the disease is but slightly altered and a fatal termination is the inevitable outcome.

This conception of thyroid conditions explains the lack of uniformly good results after sub-total thyroidectomy. The reduction of thyrotoxic symptoms will vary with the stage of the disease present when operation is performed. Those cases which continue to show signs of increased activity after operation are considered by surgeons as having had an insufficient amount of gland tissue removed. But more probably the disease had yet to run a portion of its course and lobectomy at that time had a less noticeable influence than the same operation done later. The following

quotation from a recent report on one hundred thyroidectomies is interesting in illustrating this point. The author (Mason[10]) in speaking of the best time for operation in exophthalmic goitre says, "The patient operated upon before the first crisis is eventually much better off than the one who is carried through the crisis by medical treatment and operated on later. However, the patient who is operated on early in the disease *will have a slight wave of toxicity at the time of the first crisis;* but the severity of this wave will be reduced in proportion to the fraction of the gland removed."

Advocates of early operation urge that procedure in order to prevent damage to vital organs, which frequently occurs in long-standing cases. Just how this damage to heart and kidneys is produced is one of the mysteries in the pathologic physiology of the thyroid. Means of combating it rationally are not yet at hand, so the knife is appealed to, and the temporarily diseased organ is removed permanently from the body.

A moment's reflection on this phase of the subject raises a question as to the nature of a secretion which produces such changes in vital organs. It seems logical to suppose that a normally constituted secretion which is non-toxic in small amounts should not be so toxic in larger amounts as to cause serious damage to vital organs. The body has adequate means of ridding itself of its own excess secretions. Its ability to oxidize adrenin after a short time and render it inactive is a well-known clinical fact. Consideration of this point makes it more reasonable to suppose that the damage which we know is done to vital organs is produced by an abnormally constituted product, a physiologically imperfect secretion. Such a chemico-pathologic hormone would be foreign to the organism and as harmful in its effects as an exogenous toxin.

This explanation of the damage to vital organs adds more strength to the conception of these conditions as

being due to dysthyroidism, rather than to hyperthyroidism.

Operative procedures constitute one form of treatment and must be applied in some cases, but surgery should not be regarded as the only rational therapy. It is difficult to agree with Mason's[11] conclusions that "all patients suffering from toxic adenomas or exophthalmic goitre are surgical cases." Nor is it agreeable to subscribe to the stand taken by Scott,[11] who objects to the removal of any thyroid tissue whatever. The resort to surgery, though necessary at times, is a frank admission of our inability to completely control thyroid function by medical measures. Too much reliance upon surgical aid, however, is conducive to a complacence which tends to reduce further endeavor along lines which will ultimately reveal means of restoring the thyroid to its normal function.

Those who advocate other methods often claim that there is no medical treatment for dysthyroidism. But it must be remembered that treatment consists in more than the administration of specifics. It includes everything which pertains to the patient's care and this can only be given intelligently when the patient and his case are closely studied. The attitude of indifference unfortunately assumed by some practitioners towards diseases pronounced incurable, or thought to be purely surgical, has resulted in loss of valuable clinical information on these conditions. Just such an attitude is exhibited too often toward dysthyroidism and the patient is turned over to surgery at once as though he had acute appendicitis or chronic cholecystitis. Clinical observation and rational medical treatment for a few months would not unfrequently make operation unnecessary and be productive of valuable information on the subject of thyroid dysfunctions.

The foundation of the theory of self-limitation is the observed fact that many cases of dysthyroidism get

well or improve markedly without operation. This has led many surgeons to the conclusion that such cases should be treated and observed medically for six months before being submitted to operation.

As mentioned earlier in this paper, there are certain known indirect or predisposing causes of dysthyroidism. It is helpful to consider the relation of these causes to the therapy of the disease produced. Emotional causes as fright, grief, anger, etc., cannot be regarded as producing great anatomic changes in the thyroid. Alterations of function must be the prevailing type and these are undoubtedly associated with functional changes in other endocrine glands, especially the adrenals. Cannon[12] has shown the effect which these "major emotions" have upon the chromaffin system and the marked functional changes which the whole organism undergoes as a result of such adrenal stimulation. The thyroid, in all probability, also plays an important rôle in this widespread reaction to emotional stimulation. It is possible that this gland in some cases is unable to meet the demand made upon it and reacts by elaborating a physiologically imperfect hormone with resulting dysthyroidism.

The late war has given an excellent opportunity of studying these cases and a considerable literature on the subject is available (Bérard[13], Findlay[14]). Dysthyroidism, resulting from such a cause, is usually self-limited and yields to medical treatment.

Infections, both focal and general, produce a type of dysthyroidism which also is inclined to self-limitation, improving with removal of the infection. The following brief history of a case developing after severe influenza pneumonia is illustrative.

A young married woman of twenty-eight had always had a moderate thyroid enlargement since puberty. In January, 1919, she had influenza and developed double pneumonia, which ran a very severe course with tem-

perature to 105°, delirium, marked leukopenia and cyanosis. She made an uneventful recovery but two months later began losing weight, became dyspneic, had spells of weakness and palpitation, developed a tremor and showed further increase in the thyroid enlargement with tachycardia and slight exophthalmos. The condition was obviously due to the thyroid, so she was put to bed, given some sedatives and a protein low diet. The pulse dropped from 112 to 72 in seven weeks and she improved in every respect, both subjectively and objectively.

Believing a casual relation existed between the influenzal infection and the abnormal thyroid activity, her condition was considered to be one which would subside in time and operation was advised against.

Roeder[15] reports eight cases following influenza, three of which resembled this one, in that the patients had adenomata, which suddenly became very toxic. This relation of thyroid dysfunction to influenza was noted in the epidemic of 1890 by Hale-White,[16] who mentions having seen three such cases. Todd[17] reports sixteen cases of hyperthyroidism, which developed suddenly during the convalescence of fifteen hundred patients from influenza.

The literature abounds in reports of cure or improvement in thyroid cases after removal of focal infections, chiefly located about the oral cavity. (Pern,[18] Reede,[19] Bergh[20]). Sloane[5] reports five cases of symptoms recurring after operation, which did not improve until the focal infections existing in the patients were removed.

Those cases of dysthyroidism developing during puberty or the menopause are most obviously ones which can be expected to run a definite course and then subside. Thyroid activity is a part of the general readjustment of the whole endocrine system. Such cases obviously should be given medical treatment as long as

they show any improvement or even remain stationary. A better understanding of the interrelation of the endocrine glands will undoubtedly reveal means of treating these cases rationally without resort to surgery.

The rationale of medical treatment consists in carrying the patient over the period of abnormal thyroid activity with as little damage to vital organs and the nervous system as possible. To do this, rest in bed is prerequisite with the use of sedatives if indicated. This gives the heart a minimum of work and invariably is accompanied by a satisfactory decrease in the pulse rate. Stimulation of the thyroid also is avoided by making no demands upon it. The diet should be high in caloric value to prevent loss of weight, which is consequent upon increased metabolism. A reduction of proteins is desirable as tachycardia is diminished on a protein low diet. Alkalinization to combat the usual tendency to acidosis is advisable.

Basal metabolism estimations should be made at regular intervals of about two weeks in order to determine the rate of improvement. This is rapid at first but gradually declines till it remains stationary. At this stage Roentgen irradiations may be tried if thought advisable, depending upon the type of dysthyroidism. Scott[11] advises strongly against Roentgen therapy believing there is danger of altering the thyroid's function to such an extent that return to normal is impossible, thus accomplishing the undesirable effect of irreparable loss comparable to operative results. The excellent results obtained, however, by this form of treatment recommend it highly. Care should be taken to check the result of each irradiation by careful clinical observation and basal metabolism estimations. (Means and Aub[21].)

Although, according to Hoskins,[22] the function of the thymus is unknown, still the frequent association of a persistent and hypertrophied thymus with dysthy-

roidism suggests that it probably plays some rôle in this disease. The power of the Roentgen rays to affect thymus as well as thyroid hypertrophy, is a strong point in favor of their use. (Holmes & Merrill [23].)

In addition to the probable involvement of chromaffin and thymus tissue in dysthyroidism, as already mentioned, there is the well-known fact of anterior pituitary hypertrophy following thyroidectomy, all of which add support to the contention that it is not a disease of the thyroid alone. Bertine[24] found that out of 134 cases of the thyroid disease at least 60, almost half, presented features indicating disturbance in other endocrine glands. It becomes apparent that no endocrine gland "exists unto itself alone." Nowhere in the realm of medicine is there a better illustration of the dictum, "There are no pigeonholes in nature," than in diseases of the ductless glands. This complexity makes their study and treatment a difficult problem, one which internal medicine alone may solve because, in its application, no gland or part thereof is removed from its sphere of activity, no matter how abnormal its function may be at any given time.

Recapitulation: Dysthyroidism is a self-limited disease in which perverted function is the dominant feature and in which other endocrine glands play more or less important rôles. Rational therapy should aim to carry the patient through the course of the disease with as little suffering and permanent disability as possible. Individualization is necessary in each case, and this is only possible through careful clinical observation. Such intensive study of every case will progressively unravel the mysteries of thyroid dysfunction and thereby render its therapy more and more rational.

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XI

HYPERTHYROIDISM WITH ORAL SEPSIS: A CASE REPORT

By Dr. Florence Stoney, Bournemouth, England

The following case is particularly instructive, even now, when many doctors still do not concern themselves with the condition of a patient's teeth, and when in face of several years' experience many others still deny that pyorrhea can cause hyperthyroidism, or that the consequent D.A.H. (disordered action of the heart) does occur with badly-wounded men, as well as in the unwounded. Unfortunately, if a man has a serious wound, many times no notice is taken of this "neurotic" condition, and he is left to the comparative seclusion of his bed to recover a grip on himself if he can.

It is very cheap and easy to say that the "X-rays only act by suggestion," but no proof is brought forward, whereas, the microscope definitely proves that glandular tissue, when exposed to the rays, changes and atrophies.

Certainly no amount of suggestion exerted on the patient, whose case is briefly outlined below, by those in charge of him, would have cured his D.A.H. (disordered action of the heart) until the more radical methods were resorted to.

Case: B. L., private in the Royal Scots, age 23, with 7 months' service, was wounded in the left buttock and back at Hooge, Belgium, on Sept. 25, 1915.

The bullets were removed at a Canadian hospital in France, the wounds being badly septic.

Oct. 20, 1915—Transferred to London.

Oct. 21—A skiagram showed a comminuted fracture of the left ischial tuberosity.

Nov. 19—As they were still discharging, the two wounds were opened up, and much dead bone removed. Temp., 103° F. shortly afterwards.

Dec. 12.—Temperature normal, wounds healthy, general condition very unsatisfactory.

Dec. 28—The dentist was asked to see the patient. He did nothing but advised extraction *when the general condition was better.* (He did not suggest that the pyorrhea and oral sepsis were primary to the heart condition, and, therefore, must be dealt with first if the patient were not to die.)

Dec. 30—Very ill, indeed, no albumen, no signs in chest. Left foot swollen for two days.

Dec. 31—On the danger list; he turned blue and faint even if moved in bed; put on digitalin and brandy. The surgeon of his ward came to the X-ray Department, of which I was in charge, and asked me to see him and "do anything I could for him, as he was going to die, and there was nothing further to be done surgically."

I found the patient very weak, emaciated and highly excitable. The wounded hip was kept flexed, the wounds looked healthy. The left leg and foot were edematous, with tenderness of the popliteal vein and evident thrombosis.

The heart was slightly dilated, sounds feeble and toneless, no murmurs, pulse 138 (in the ward), 158 in the X-ray room. No goitre, no exophthalmos; tremor, perspiration and general nervousness all marked. Abdomen doughy, and constipation marked. Teeth much decayed and very septic, the mouth condition being about as bad as possible.

I diagnosed his general condition as being really due to hyperthyroidism, much aggravated, if not actually caused by the extreme oral sepsis. I may say that I

was not upheld in this diagnosis by any other member of the staff, except possibly the surgeon who had put me in charge of the case, who went so far as to say the heart condition was not dependent on the wound, though the thrombus was.

Diagnoses varied. The officer in charge of the hospital diagnosed "cardiac trouble but did not think of thyroid." One surgeon "did not think it was a thyroid case." The senior surgeon and the heart specialist both diagnosed "septic myocarditis; but did not think it was due to the thyroid."

Jan. 1, 1916—Patient was carried, bed and all, to the X-ray room, as he was too weak to transfer to a stretcher, and given a full filtered pastille dose of X-rays to each lobe of the thyroid. P., 158 (lying down). At the same time a vigorous effort was made to clear up the oral sepsis by wiping round the gums frequently with strong tincture of iodine.

Jan. 3—Pulse distinctly better, 112. Tinc. iodine continued.

Jan. 7—Second dose of X-rays, looks brighter, edema now reaches to left mid-calf, tubes out of wound. P., 120, slightly irregular; perspiration very marked, mouth cleaner.

Jan. 14—Fortunately, an abscess in the left buttock required opening under general anesthesia. The bone was scraped and, at the same time, several septic dental stumps were removed. In spite of his very weak condition the patient took open ether well, the pulse being 136 at the beginning and only 120 at the end of the anesthetic.

Jan. 26—Third X-ray; and from that time on X-rays were given at about weekly intervals till the end of April, finally ending May 27, 1916, with the 17th treatment.

The digitalin and brandy were discontinued early in the case. The local use of tict. iodine was persisted in till April 12th, when the mouth appeared clean.

General Condition—Even by Jan. 7th he looked brighter and not so certain to die.

By Feb. 10th he was brighter, temperature normal, always in pain, but wound closing, less perspiration, less tremor, heart nearly regular, stronger. P., 134 over heart when lying down, some beats did not get through to the radial. At this time cigarettes cut down to five per diem.

Feb. 16—No tendency to faint now. P., 114 (lying). R. leg normal, L. leg still flexed and swollen.

Feb. 29—P., 104, lying down (86 in ward); no dilatation of heart; first still toneless. Getting fatter, tremor and perspiration slight, wounds healing.

He was shown at a clinical meeting and pronounced to be "a resurrection."

March 9—In a bath chair. P., 116 (sitting); upper back wound still open.

March 15—P., 104, regular (sitting).

April 8—All healed. P., 86 (sitting), 76 (lying). First cardiac sound stronger and regaining tone, slight tremor, no perspiration. He is walking on crutches, the left leg much crippled and left foot edematous.

Eating well, sleeping well, not nervous, mouth clean, bowels regular.

April 14—P., 76, sitting; no symptoms at all of exophthalmic goitre today. Left leg is getting straighter, still flexed and adducted at the hip joint.

Expert massage and movements were now begun, at first the patient was in great pain and could not put his foot to the ground, but after 28 treatments there was less shortening and he could get good weight on his foot without pain as he walked.

May 11—Trace of tremor. P., 92.

May 27, 1916—Well in himself, putting on flesh. P., 80, both standing and lying down, no tremor, no perspiration, no nervousness—he has but few teeth, but he eats well.

He left the hospital and was discharged from the army.

Oct., 1917, or 18 months later, he wrote that he was perfectly well and had resumed work as a pitman in a mine in Scotland.

Events would seem to show that the combination of stopping the source of the poison by radical daily cleansing of the mouth and gums, and treating the overstimulated thyroid by X-rays to cause partial atrophy, in this case turned the balance between life and death, the myocardium gradually recovering its tone and functioning correctly *when no longer poisoned.*

The tonelessness of the cardiac first sound is markedly characteristic of hyperthyroidism. Cases such as this might be recognized and diagnosed earlier as to the true source of the symptoms; in which case treatment might be started at a much earlier stage. It is only fair to add that without excellent nursing this man would have inevitably succumbed.

XII

CLINICAL OBSERVATIONS ON THE USE OF ANTERIOR PITUITARY AND THYROID SUBSTANCES IN GOITRE AND NEURASTHENIA

By Leigh F. Watson, M.D., Chicago, Ill.*

The purpose of this paper is to report the results secured with pluriglandular medication—a combination of anterior pituitary substance with thymus and thyroid—in 75 cases of goitre and neurasthenia.

Experimental Studies

A disturbance in the endocrine balance is the generally-accepted cause of the symptoms of toxic goitre as well as of neurasthenia. This hypothesis is supported by the pathological studies of Louis Wilson, of the Mayo Clinic, who has definitely proved the constant association of exophthalmic goitre with primary hypertrophy and hyperplasia of the thyroid gland. His associate, Kendall, has isolated from the thyroid an active hormone, called "thyroxin," which, when injected into a normal person, increases pulse-rate, vigor, metabolism and nervous irritability.

It is well known that physiological enlargement of the thyroid—a compensatory hypertrophy—is most frequent in women at puberty, during pregnancy, and at the menopause. Kimball and Marine have demonstrated that the feeding of sodium iodide to children living in goitrous geographical belts, will lessen the fre-

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* *The writer of this essay received the first prize of $250.00.*

quency of the occurrence of thyroid enlargements as the individuals approach "the goitre age." When goitre already has developed, the administration of an iodide will cause it to diminish in size, in over half of the cases, and in many instances the glandular enlargement will disappear entirely.

The recurrence of a goitre after operation is believed to be due to compensatory hyperthrophy of the remaining portion, which enlarges in its effort to furnish sufficient of its hormone to supply the demands of the system. Patients who have submitted to partial thyroidectomy will be less liable to recurrence when kept under prolonged observation and iodide or thyroid extract given when indicated, to prevent the secondary hypertrophy and hyperplasia, just referred to.

QUININE AND UREA INJECTIONS

A majority of the goitre patients mentioned in this report came to me suffering with the usual symptoms of hyperthyroidism. To control the hyperthyroidism and lessen the abnormal amount of thyroxin that is entering the blood, a portion of the hyperactive gland is destroyed, by making several injections of quinine and urea directly into the anterior portion of the tumor. The strength of the quinine and urea solution varies, depending on the type of the goitre and character of the symptoms. Only one injection is given at a treatment, which is repeated at two to six-day intervals. Ten to twenty infiltrations usually are required to produce marked improvement in the general symptoms. It is important that only a few minims of the concentrated solution be injected at a time. The changes in the thyroid at the point of injection are the phenomena of inflammation followed by swelling, hyaline degeneration, and finally necrosis of both epithelium and stroma. As soon as sufficient thyroid has been destroyed, which is shown clinically by a gain in weight, slowing of the

pulse, and lessening of the tremor, insomnia and nervousness, the injections are stopped, and the patient is placed on a modified rest cure and a lacto-vegetarian diet. Anterior pituitary is given to improve the general symptoms of exhaustion that accompany toxic goitre, and the addition of small amounts of thyroid tends to prevent secondary compensatory hypertrophy of the untreated portion of the thyroid gland.

SOME REMARKS ON NEURASTHENIA

The symptom complex that we call neurasthenia, or nervous prostration, was known to the ancients, and is well described by Hippocrates. In few diseases is the treatment more unsatisfactory, because of the multiplicity of misleading symptoms and the difficulty of controlling the patient.

The typical neurasthenic almost always has a disturbance of the function of the thyroid gland. The blood pressure usually is low and the circulation poor. Frequently the activities of the internal organs are impaired, although there may be no discoverable organic disease. Mental exertion, even of the simplest character, often causes so much weariness and exhaustion as to be prohibitive. A vasomotor paralysis, sometimes present, allows chillings, flushings, cold or burning hands and feet, drowsiness when patient is up, wakefulness on lying down, hence insomnia. The nutrition may be fair, or good, and the weight may be normal. There may be more or less tingling and numbness of the extremities. Thymus disturbance is manifested by weakness, dyspnea, nervousness and obstinate constipation, and deficient calcium metabolism—as in conditions like rickets, marasmus, etc.

The indications for the administration of anterior pituitary substance, according to the recent studies of Engelbach and others, are undergrowth of bones, amenorrhea, metorrhagia, dysmenorrhea, sterility,

subnormal temperature, slow pulse and relatively low blood pressure and fatigability. However rapid pulse and high blood pressure is not a contraindication to the use of anterior pituitary substance. I recall a case of pronounced neurasthenia with a systolic blood pressure of 160 mm., pulse 110, and a temperature of 97-48° F. This patient weighed 182 pounds, and I believed that most of her symptoms were due to the same fundamental causes as the obesity. I prescribed small doses of thyroid with sedatives, and she steadily lost in weight, but the neurasthenic symptoms became more pronounced. As soon as anterior pituitary was added to the thyroid, her neurasthenic symptoms promptly disappeared; the systolic blood pressure dropped to 115 and the pulse to 80, while her weight remained at about 180 pounds.

CLINICAL EXPERIENCES

Space will permit the report of only a few of the case histories in this series of 75 patients treated with anterior pituitary and thyroid.

Case 1. Mrs. G. W. M., aged 66, for 40 years had had a small goitre of the left thyroid lobe, which had caused no trouble until 1917, when she noticed an increase in its size, accompanied by such symptoms as marked tremor, nervousness and insomnia. At examination in January, 1919, her pulse was 120, systolic pressure 150 mm., diastolic 85 mm. There was some dyspnea, loss of weight and the fatigability was marked. I injected quinine and urea into the thyroid gland and prescribed the anterior pituitary preparation, one standard sized dose to be taken daily. One year later the goitre had reduced one half in size, the symptoms of hyperthyroidism had disappeared and she was in good health.

Case 2. Miss G., aged 23, came under my observation in 1918 suffering from severe exophthalmic goitre of one year's duration. The tumor was large, involving both lobes of the thyroid and the isthmus. The pulse was 140, menstruation was irregular and scanty, and

there was some loss of weight. I injected quinine and urea into the thyroid gland and prescribed anterior pituitary compound, one capsule to be taken daily for one week in each month. Taking the even small dose of thyroid (one twelfth of a grain) more frequently aggravated the symptoms and caused loss of weight, while using it intermittently with the pituitary had a beneficial effect. In six months the general symptoms were relieved, and the goitre reduced one third. She had gained 14 pounds in weight.

Case 3. W. T. C., aged 50, had a small goiter of eight years' standing. It had caused no symptoms and had remained stationary in size until following an attack of influenza in January, 1919. At this time she came to my attention, suffering with toxic goitre, aggravated by the symptoms of the menopause. The pulse was 130, systolic pressure 150 mm., diastolic 100 mm., temperature 100 deg. F., pains over both ovaries, marked insomnia, tremor, nervousness and loss of weight. Quinine and urea injections were given into the thyroid and the patient was placed on small doses of posterior pituitary and thyroid. This increased her symptoms and shortly after had to be discontinued. The thyroid alone was then tried, and this had to be abandoned also. Finally the anterior pituitary combination was prescribed, one capsule to be taken daily, and she has gained in weight, her symptoms are relieved and the goitre has been reduced one third.

Case 4. Mrs. B. F. M., aged 34, noticed that she was developing a goitre following parturition in 1914. She came to my attention in May, 1920, when she presented a small toxic goitre involving both lobes, together with symptoms of neurasthenia, headache, loss in weight, and fatigability. I prescribed posterior pituitary and thyroid. This aggravated the symptoms and I substituted anterior pituitary compound, one dose to be taken twice daily. Under this treatment she has noticed a reduction in the goitre, and decided improvement in her general health, her headaches have disappeared and she has made a slight gain in weight.

Case 5. Mr. D. C., aged 31, noticed goitre with severe exophthalmic symptoms four months previous to examination March, 1920. During this time he had lost 35 pounds in weight. Pulse 140, systolic pressure 145 mm.,

diastolic 70 mm., and temperature 100 deg. F., marked insomnia, nervousness and tremor, diarrhea most of the insomnia, and anterior pituitary compound one gland lobes. I injected quinine and urea into the thyroid and prescribed small doses of sodium bromide for the insomnia, and anterior pituitary compound one capsule daily. Three months later the patient had gained 10 pounds in weight, the pulse was down to 108 and the general symptoms had improved as the goitre was reduced in size.

Case 6. Mrs. J. F. M., aged 23, had had goitre for two years, evidently caused by pregnancy. Examination May, 1920, disclosed symptoms of severe exophthalmic goitre, including scanty menstruation, loss of weight, marked insomnia, nervousness, diarrhea and tremor, pulse 160, systolic pressure 150 mm., diastolic 85 mm., temperature 100 deg. F. There was a moderate edema of the ankles. Quinine and urea injections were made into the thyroid gland and the patient received the anterior pituitary preparation, one capsule daily. She improved rapidly. Now, four months after treatment, the symptoms have disappeared and she has gained 15 pounds.

Case 7. Mrs. S. M. H., aged 29, suffered from severe exophthalmic goitre for two months previous to examination May, 1920. During this time she had lost 20 pounds in weight. Marked insomnia, nervousness and tremor. Pulse 130, temperature 99 deg. F. I injected quinine and urea into the thyroid and prescribed the same anterior pituitary formula, one capsule to be taken daily. In four months this patient has gained 18 pounds, 7 pounds in the last three weeks. The goitre has reduced in size, the symptoms of hyperthyroidism are very much better and she is again doing her housework.

Case 8. Miss E. B., aged 19, examination April, 1920. Complained of fatigue, nervousness, loss of weight, insomnia, fatigability and other symptoms of neurasthenia following scarlet fever two years previous. Pulse 90, systolic pressure 100 mm., diastolic 65 mm., temperature 97½ deg. F. I prescribed the anterior pituitary formula, one capsule to be taken twice daily. She gained steadily for one month when her weight became stationary and she was instructed

to take only one capsule a day. She has gained a pound a week since the dosage was reduced, and now, 5 months after beginning treatment, writes that she is in better health than she has been in four years and considers herself cured.

CONCLUSIONS

1. In this series of 75 cases only three patients could not tolerate one twelfth grain of thyroid extract (U. S. P.) daily. Two of these were severe exophthalmics in whom probably I had not destroyed enough of the thyroid and the third patient was a neurasthenic with no thyroid enlargement or symptoms of hyperthyroidism. She was inclined to obesity and ran a subnormal temperature. One twelfth grain of thyroid was sufficient to produce a headache that would last twelve to twenty-four hours. This last individual is probably a case of thyroid idiosyncrasy.

2. It is believed that the administration of thyroid after partial thyroidectomy or destructioin of a portion of the thyroid by injection, will lessen the tendency of these patients to develop recurrence, which is probably due to secondary compensatory hypertrophy and hyperplasia of the untreated thyroid.

3. I believe that the product of the anterior pituitary lobe gives better results in the after treatment of toxic goitre than the posterior pituitary principle.

4. Thymus is recommended by several writers as having a beneficial effect in hyperthyroidism and the presence of one grain of the desiccated gland in this formula evidently adds to its value in these cases.

5. Generally speaking the best results will be secured by giving all ductless gland extracts over a period of six to twelve months.

6. If the symptoms of a patient with toxic goitre are aggravated, even following small dosage, or if she loses weight under anterior pituitary and thyroid, it is evi-

dent that she does not need the thyroid, and the anterior pituitary substance should be given alone.

7. Other glandular extracts are indicated in certain patients who show a hypofunction of other ductless glands. The addition of ovarian substance usually is advisable for women at the climacteric.

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XIII

THE SPHYGMOMANOMETER AND THE ENDOCRINES

By R. O. Butterfield, M.D., Denver, Colo.

In the days of our childhood, the old-fashioned family physician used to judge our fever by the pulse rate, and by the sense of touch determined the quality of the pulse or the blood pressure. He might or might not have used the stethoscope. Then came the clinical thermometer and other instruments of diagnostic value, but without a doubt the most important one of recent years is the sphygmomanometer.

After a physician becomes accustomed to the frequent use of the last-named instrument, he will find it more valuable in diagnosis than the clinical thermometer; also as an indicator of the progress of the condition present, as well as a means of determining the prognosis of many diseases. He will find the indications for the use of the sphygmomanometer, generally speaking, more frequent than those for the stethoscope and that when both instruments are used the findings of the former will often be more valuable than those of the stethoscope.

The knowledge gained in the last decade or two by means of the sphygmomanometer regarding blood pressure in various diseases, is immense and in some ways is rather surprising. Sometimes, too, this information is rather contradictory to what might have been expected from other conditions present.

In the minds of the laity and, for that matter, with a large number of physicians, *high* blood pressure is the only thing to be watched for, without realizing that a hypotension for the age average, or a steadily falling pressure of the blood, indicates an atonic state, a toxemia, a concealed hemorrhage or some other grave condition. They are also ignorant of the fact that hypotension is of more common occurrence than hypertension.

BLOOD PRESSURE IN ACUTE INFECTIOUS DISEASES

If we make a comparative study of the findings accompanying acute infectious diseases, we find some characteristics common to all, others common to many, and were it not for the uncommon characteristics, we could not distinguish many of these diseases from one another. For instance, recall how many acute infections begin with a chill, followed by a fever, with the rise and fall of temperature peculiar to the particular disease.

In most infections and also in most chronic conditions (with a few exceptions which I will mention later), we find an arterial hypotension. Usually, with the onset of fever in acute infections, goes a temporary rise of blood pressure. In some instances of infection when I was called during the chill and had my sphygmomanometer with me, I have found the pressure to be rising even then. Undoubtedly if we could be able to secure reading more frequently at this stage, we should find the blood pressure changes of much interest and practical value.

While the fever may keep up for days, within two or three days after its onset, the blood pressure begins to fall and continues to do this until it reaches a point considerably below the normal for the patient's age.

As an exception in infectious diseases, might be mentioned meningitis, in which hypertension is more often

found instead of a hypotension; this is also true of several chronic conditions, especially those involving the kidneys and heart, and in some cases of poisoning, as from lead.

The chill and rise of temperature mentioned above are due to the reaction of the system to the toxins produced, by the growth and metabolism of the invading bacteria. It may be that these toxins stimulate the adrenal glands directly, and these, as a result, soon throw out their specific hormones more abundantly. The adrenal medullary secretion acts on the muscle tissue of the heart and of the blood vessels, causing contraction, resulting in an increased blood pressure. It has been proved that the blood pressure rises and falls in direct proportion to the amount of adrenal secretion in the system. Another theory regarding the adrenal response in such circumstances, which may seem as good to some, is that the system, finding itself invaded by the toxins, automatically brings into play certain nervous stimuli which increase the adrenal secretion; but however it comes about, we know that this increase persists for a time at leasat.

We have known for years that the initial increase of blood pressure in infectious diseases was an effort on the part of nature to produce greater detoxication and elimination. Later, the heart and the blood vessels seem to lose tone and the system is unable to maintain the blood at its higher pressure, and we find at times, with this decrease, that the organism cannot keep up the proper excretion of toxins, and, unaided, it would be but a matter of time in many cases when the patient would be overcome by them. Whether the resultant accompanying hypoadrenia is caused by a lack of secreting action of the adrenal glands, or a leak from the system of this secretion, is a mooted question; but we know that the lack exists, because by supplying the adrenal secretion, or the gland substance itself, the

blood pressure rises, elimination is increased, and a condition of greater vigor is recognized.

In times past, when it was observed that the system was being overwhelmed by toxemia, there would be begun what in medical parlance we call "stimulation," and strychnia, digitalis and other heart-whips would be applied; now as we shall see, we investigate the adrenal aspects of the case and spare and encourage these little glands when necessary.

Purgation at the outset of most infections is rational therapeusis, as it is an attempt to use outside agents to eliminate poisons from the system. But purgation must not be kept up indefinitely; and, furthermore, it accomplishes only a part of the work of elimination. The kidneys, skin, and lungs each must do their part and unless the blood pressure is up to normal and each organ given the requisite amount of blood, their full quota of work cannot be accomplished.

Many discoveries have been the result of accident, a mere stumbling onto something useful without any directing force along the path. On the other hand, many discoveries are the result of hard study and research. It has been the experience of a large part of the profession today, that our lecturers on physiology, not so very many years ago, coming in their discussions to the subjects of the thyroid, thymus, spleen, or adrenal glands, would generally, after a brief anatomical description, dismiss the subject with the remark, "One of the ductless glands; function unknown."

The work done on the hormone-producing organs and the knowledge regarding them that has been gained as a result of much effort by many workers within the past score of years is vast, both in quantity and value. These discoveries must be classed with all the great discoveries of physiology, and are of even greater importance to medicine than some things that we formerly considered of first importance. This is because of

the additions to our therapeutics made possible through this new knowledge.

THE LABORATORY VS. THE CLINIC

The stigma of empiricism that some have tried to attach to the work of the investigators along the line of endocrine therapeutics, is puerile and this is decidedly apparent in the light of results that we are getting every day with organotherapy.

Advance along these lines only can be accomplished by clinical proving; the laboratory must give way to the clinic.

Far too many physicians still look too literally on a disease as an entity, something separate from the body, which "attacks" the patient; but they do not look upon "dis-ease," as a "dis-comfort," a malcondition of the body caused by the presence in the system of something which should not be there, as, for instance, the toxins in infectious or chronic diseases; or the lack of something that should be there, as, for instance, the lack of the thyroid secretion in myxedema.

Too many times we forget that all the physician can do is to assist nature in ridding the patient of his "dis-ease." We can help nature sometimes by antidotes or antitoxins, or by neutralizing poisons; and by vaccines, we may assist nature to destroy invading germs. Then we can be very helpful still further by assisting in the elimination of poisons from the system. Here is one place where organotherapy comes to our assistance and if we are wise we will avail ourselves of its aid. Should the "dis-ease" be due to the lack of the secretions of a ductless gland or glands, organotherapy will be just as beneficent as it is physiological in helping us to assist nature by supplying the lack.

It has never been my lot to be able to work out in the physiological laboratory any of the theories or

problems regarding the ductless glands and their products, but it has been my great privilege and pleasure to demonstrate, clinically, the results of the study and research of some of the master minds of today and of the last two decades, who are giving their time and powers to the investigation of the endocrine glands. I am glad to offer my testimony in their favor.

The reason why I use organotherapy in my practice can be told in the five words BECAUSE I GET GOOD RESULTS. The story of "HOW" I came to use the endocrines more and more frequently, would take much longer, yet a few words about the "WHYS" and "WHERES" may be of value to others who have not made a thorough trial of these adjuvants, which many times are virtually specifics. Sometimes the "why" is hard to answer, but if I find that a remedy does the work, I do not refrain from its use merely because I cannot find an explanation for each step of its *modus operandi.*

ADRENAL THERAPY IN DRUG ADDICTION

In a case of morphine addiction that I had under treatment in 1908, I found an unusually low blood pressure. From later experience, I have found that is what we must expect in most of these addicts unless possibly there is a severe complicating nephritis. The systems of these patients always are in a state of greater or less intoxication on account of the diminished elimination, and in all of these cases elimination is the prime key to successful treatment. In the case mentioned, in addition to catharsis and diuresis with the usual remedies that I had been in the habit of using before, I tried one of the preparations of adrenal gland that was on the market. It gave me such satisfactory results that I began using it in other chronic conditions having low blood pressure and in which elimination was needed, and there are comparatively few cases

that do not have both of these clinical characteristics. It was only a step for me to discover that a related condition existed in many acute infectious diseases, and that the lowered tension and resistance prepared a fertile soil for the development of the tubercle bacillus.

With just as much reason we can go a step further and say that anything that produces a hypotension of the circulation may be a predisposing factor in any infectious disease should exposure to that infection take place at such a time.

That the syndrome known as hypoadrenia exists in these conditions we know well. What, then, should be our line of treatment? Two methods of attack are suggested. First: To stimulate the adrenals so that they will produce more abundantly. This is not logical treatment because those glands probably have been overstimulated already in order to supply the demand caused by the falling blood-tension. This has caused overwork and they have at least temporarily failed. The second method is the logical one. It is to supply the deficiency from outside by applying the principles of organotherapy. With this method we get results. We secure a better heart action, a higher blood pressure and far better elimination. Not for a moment would I have one think that all I believe we have to do is to raise the blood pressure, but what I want to emphasize here is that the raising of the pressure of the blood is of great importance in curing the patient, provided a hypotension exists.

The administration of adrenal substance, with or without synergists, not only provides immediate systemic effects, but it gives the overworked adrenals of the patient a chance to recover themselves so that later they can take up their work and perform their normal function again.

If we take up the phase of hypotension in chronic diseases of non-infectious origin, there is very little that could be said that has not been said already in general regarding the similar conditions in acute infectious diseases. In both circumstances patients are suffering more or less from toxemia, caused by the bacterial poison, produced in their development. In non-infectious chronic conditions, on the other hand, the toxemia is caused by the retention of the products of metabolism or as the result of malmetabolism. In both classes, generally speaking, we have poor elimination, caused in part, at least, by the accompanying low blood pressure. [Elsewhere the reviewer has shown that the opposite is equally true, i. e., that the deficient chemistry favors the hypotension.—H. R. H.] Then, of course, a part of the treatment in both of these classes of diseases becomes the same—efforts to increase elimination as nearly as possible up to normal, and direct support of the played out glands by the use of adrenal substance with the other endocrines by measures which act on the urinary and alimentary tracts.

ENDOCRINE ASPECTS OF CANCER

For over a quarter of a century, the two diseases that have received my greatest study and attention are tuberculosis and malignant growths. With cancer, I am no longer looking for a germ as the causative factor, but I consider cancer from the start to the end as a condition due to autointoxication. The breaking out of the sore at the site of an old bruise or continued irritation is not the beginning of cancer. The foundation for the new growth was laid months or even years before in chronic autointoxication. If this underlying, precancerous condition had not existed, the site of the bruise or irritation would not have become the site of the cancer, for where one cancer sore develops at a

point of irritation, dozens of people have received a similar or greater irritation at the same point without a cancer resulting.

Then the correct treatment of cancer resolves itself into two parts: destroy the local condition and free the patient from the autointoxication. Surgical treatment unaided is ineffectual, as shown by the large number of recurrences. The apparently successful cases are those who by good fortune, either by design or accident had their waning blood pressure increased and in whom elimination was invoked to the limit. Thus adrenal substance became an important adjunct in the treatment of cancer. But it is not the only endocrine we should use. While some use trypsin internally as well as locally and recommend it highly, and undoubtedly it is of great value, dessicated spleen has given me better results. In fact, we have reason to believe that the spleen stimulates the pancreas, thus increasing its trypsin output. While trypsin is supposed to have a direct antimalignant effect as a digestant of cancerous tissue, the spleen substance is more of a reconstructive, particularly a hematinic. Other organotherapeutic materials will work in well in the treatment of cancer, depending on the organ which is affected by the malignant growth, and the associated general condition including the functional capacity of the ductless glands.

SOME CONSIDERATION ABOUT HYPERTENSION

In considering the other phase of blood pressure, hypertension, a number of elements must be studied in order to reach any definite conclusions. The hypertensions are easily classified for study into the organic and the functional.

In the first class, the immediate cause lies in a pathological change in some vital organ, as, for instance, in the kidney as an interstitial nephritis; or in hypertrophy of the heart, or in the arteries as in arteriosclerosis.

In these organic cases, while the blood pressure may not be so high as in the functional type generally, yet the prognosis is grave so far as a complete clinical cure is concerned and with a large number of these patients, the organic condition is a menace to life.

The aim of treatment must be directed to the amelioration of the symptoms and the comfort of the patient. Drugs are of some value it is true, yet while not promising to do the impossible, organotherapy will do wonders in some of these cases in alleviating conditions. Each case must be studied individually, and the glandular products chosen accordingly; on the other hand a renal case may be benefited by renal organotherapy, while, on the other, antagonism to adrenal hypersensitiveness by pancreas substance may be just the thing. As time elapses better and better results from the endocrines are to be expected in treating cases of hypertension.

When we undertake the study of a case of hypertension of functional origin, we can do so with the greatest assurance of success for we are dealing with a condition the cause of which we have a better chance of removing, and this is generally a toxemia—cellular, alimentary or dietetic; while in the hypertensive case with an organic basis, we are dealing with a morbidly changed anatomy, which can be restored toward the normal only in a degree. Of course we must recognize the fact that functional cases may go on for a longer or shorter time and morbid changes may take place which will put these cases into the organic class. In passing, we might say that the probability is, if we are able to trace the trouble back to the beginning in all the cases of organic hypertension, we should find that it began initially in a toxemia as, for instance, the bacterial toxema of diphtheria or scarlatina which resulted later in a nephritis.

While the toxemia causing hypertension may be generated within the body, as was just mentioned in diphtheria or scarlet fever, it may come from outside as in lead-poisoning. The lack of certain glandular secretions also may cause hypertension. This is particularly noticeable after a double ovariectomy in a young woman or after the menopause in older women. Of course the obvious treatment is to supply the ovarian and allied principles to the patient. [Another not common factor in bringing about a typically endocrine increase in the blood-pressure is concerned in the condition known as "infiltration" which so uniformly accompanied thyroid insufficiency. This theory has been quite fully outlined in a paper of my own, which will follow this essay.—H. R. H.]

SUMMARY

By way of summary, we should remember that hypotension is met with more frequently than hypertension. Hypotension, accompanied by muscular and cardiac atonia, generally is due to toxemia. The treatment consists of elimination by all the emunctories. Glandular products will form a part of the treatment, especially adrenal combinations or substance. Hypertension is due, in most cases, initially to toxemia, producing organic changes in some organs as heart, blood vessels or kidneys. While the prospects of clinical results are not so good, elimination is the key to treatment, with properly chosen organotherapy to retard excessive secretion of the adrenals or to modify the secretion of any gland as the thyroid, whose secretion may be stimulating the adrenals.

XIV

THE RELATION BETWEEN HYPOTHYROIDISM, INFILTRATION, AND HYPERTENSION

By Henry R. Harrower, M.D., Glendale, Calif.

The functional aspects of high blood pressure are being given increasing attention in current medical literature, and it is very clear that many members of the profession are coming to the conclusion that there is a fundamental underlying cause of the usual syndrome associated with high blood pressure that is not connected with hardened arteries, impermeable kidneys, or changes in the heart itself.

Quite recently a prominent Dutch internist lends emphasis to this particular subject in the following words: "We have no grounds for the assumption that high blood pressure is always secondary to heart, kidney, or vascular disease. It has no more significance than the discovery of a murmur or hardening of a normally soft organ. Because we can measure the blood pressure we have paid too much attention to it and hidden our ignorance behind the term 'essential hypertension.' The rise in blood pressure is merely one element of a morbid series which has to be regarded as a whole." [1]

Another recent interesting communication on the subject was made by Dr. L. F. Barker of Johns Hopkins at the last meeting of the Ohio State Medical Association.[2] He calls attention to the fact that high blood pressure appears to depend chiefly upon a narrowing of the lumina of the arterioles in the precapillary areas.

It is believed to be, at first, functional and caused by hypertonus of the arterial musculature, but later on it assumes a partly organic character, the result of changes in the arterial walls. Barker believes that the different types of chronic arterial hypertension probably represent different stages in the development of the same fundamental process which may advance with variable rapidity and with variable associated involvement of cardiovascular, renal, cerebral, and other structures in different cases. This author then goes on to call attention to the general changes which are fundamentally responsible for the condition of high blood pressure, and he states that in order to prevent the development of this pathologic process underlying high blood pressure "one should first get himself well-born without constitutional inferiorities" and then should avoid intoxications and infections and live a well-balanced life, so ordering his activities that he can satisfy his physical, economic, social, educational, esthetic, and ethical desires in a well-balanced manner.

For many years it has been considered fundamental that toxemias favored high blood pressure and that they did so first by causing an overactivity of the circulatory system resulting in changes in the heart and blood-vessels. Also that the toxemia irritated the actual glomerular tissue of the kidneys and, therefore, made changes which tended toward what the French have called "renal impermeability." Later our ideas have veered a little, and it is now considered possible and probable that irritation of the blood-pressure-raising mechanism of the adrenal glands, by means of the poisons produced in the alimentary canal and elsewhere, results in an increased activity of this pressor mechanism and in this manner produces a functional high blood pressure.

Be this as it may, there is no doubt that high blood pressure is merely a single manifestation of a serious

comprehensive underlying change in the chemistry of the body, and it is proposed in this short paper to direct attention to one factor which has not been given the attention that its imporance deserves and to connect it with the etiology as well as the treatment of functional or essential hypertension.

There have been a number of papers in the literature of the last five years calling attention to clinical experiences with the use of thyroid extract and other organ extracts as a means of reducing high blood pressure. A number of reports, including that of Cummings of Los Angeles[3] and Bandler of New York,[4] speak highly of thyroid therapy as a means of modifying an excessive arterial tension. As far back as twenty years ago, before sphygmomanometry was developed, Eugene Hertoghe of Antwerp[5] called attention to the changes wrought upon the pulse rate and tension by the toxemia and disturbed metabolism of thyroid insufficiency, as well as from the opposite manifestation, or thyrotoxicosis. This intelligent pioneer student of thyroid function has emphasized the importance of the condition known as *infiltration* which accompanies various forms of thyroid insufficiency. Hertoghe's so-called "myxédème fruste"—a minor form of real myxedema—is always associated with changes in the nature of cellular infiltration. Hertoghe believes that the thyroid never can be functionally inefficient without there ensuing immediately an intoxication due to the deficient function in the cells themselves which is maintained by the hormonic "setting in motion" of the cellular chemical processes. They are unable to oxidize their foods and wastes and there follows an accumulation of poisonous substances which causes serious difficulty. In this connection it may be mentioned that Slosse of Brussels[6] credits the thyroid hormones with a "deaminizing" influence and he states that the deaminizing hormone of the thyroid is responsible for the oxidization of the

precursors of the nitrogenous wastes of the body and there is good evidence to prove this physiologically and clinically.

At all events, this accumulation of cellular wastes brings about the condition which Hertoghe has called "thyroid infiltration" on well-known physical principles. We will presume that a given cell located in any part of the body—for the thyroid influence extends to every corner of the human organism—is not maintaining its normal chemical activities, that it is suffering with the condition which I have named "chemasthenia." The cellular activities are lessened and, as a result of this, the wastes of that cell are not prepared for elimination and remain behind. As a result of this there ensues an actual swelling of the cell due to the effort on the part of the body to maintain a normal osmotic tension. In other words, this increased osmotic tension in the cell draws fluids from other parts of the body, including the blood, lymph, and tissue juices, which evens up this tension and, therefore, extends the confines of the cell wall. We are in the habit of expecting an infiltration of the skin in myxedema—the very name of this condition indicates that there is an edema of the skin—and this edema or process of swelling or infiltration, as it is preferably called, is not limited by any means to the superficial tissues of the body.

It will be recalled that in Barker's paper,[2] from which a quotation already has been made, he believes that high blood pressure appears to depend chiefly on a narrowing of the lumina of the arterioles *in the precapillary areas*. What is the chief reason for the narrowing of these lumina? May it not be that the infiltrated cells which surround these prearteriolar canals or vessels are pressing upon the channels through which the blood usually flows, thereby reducing the circulation and also increasing the activity of the heart muscle which is necessary to force the blood

through these finest capillary meshes? In this connection we recall very well that another of the commonest symptoms of hypothyroidism is a tendency to cold hands and feet. The circulation of the remoter parts of the body is very much below par, and this I believe to be due to exactly the same cause as the infiltration that already has been mentioned.

I think that we have reasoned out a relation between the infiltration of thyroid insufficiency and a decreasing of the size of the precapillary vessels and this I believe to be an important mechanical factor in the cause of hypertension. It is granted that the other toxic influences which would naturally accompany so serious a change in the general cellular chemistry must exert their influence also, and it is presumed that they do so through their effects upon the adrenal mechanism and its control of the circulatory muscular tone, including that of the heart itself. If we are successful in our thyroid therapy of the minor forms of hypothyroidism we will notice quite a change in this infiltration and its results. Many symptoms of a semimechanical nature are reduced. The cells are enabled to throw off a good deal of the effete material and there is a consequent increased chemistry as indicated by the urinary findings and a loss in weight due to the removal of much of the infiltrated effete material. This being the case there is a change in the nutrition of these infiltrated areas, and the skin (and other tissues) assumes a more healthy appearance; the work of the various organs, which heretofore have been puffy, soggy, and infiltrated, is more nearly normal; the circulation is increased and this mechanical factor, which I contend is a part of the cause of the high blood pressure, automatically is reduced.

In other words, thyroid therapy in cases of hypothyroidism with high blood pressure not merely removes a part of the accumulated toxemia but at the same time

favors a change in this mechanical obstruction to the circulation in these so-called "precapillary areas."

Many remarkable clinical experiences with both thyroid therapy and various pluriglandular formulas in the control of functional high blood pressure[7] has emphasized in my own mind a very important series of therapeutic possibilities in the treatment of this condition. It is first necessary to establish the fact that hypothyroidism is present and prominent as, for example, with my thyroid function test,[8] and then we have a most rational and scientific means of treating this particular condition; and if, in conjunction with other benefits there is a change for the better in the high blood pressure, then we are pleased. It may be said in this instance that another useful means of modifying functional high blood pressure due to toxemic irritation of the adrenals is the use of the antagonistic function of the pancreas which is known to balance adrenal medullary activity. We have had a good deal of experience in the use of combinations of thyroid with pancreas substance (not pancreatin) and many times the sphygmomanometer shows encouraging changes in the systolic pressure.

XV

ADRENAL HYPOFUNCTION IN EVERY-DAY PRACTICE

By D. C. Ragland, M.D., Los Angeles, Calif.

Some years ago, when I first began to read about the ductless glands and their troubles, I was very forcibly struck with the divers symptomatology of thyroid and adrenal hypofunction. Here we find disturbances in one or more of the following parts: Hair, head, eyes, nose, ears, mouth, teeth, tonsils, respiratory system, cardiovascular system, gastrointestinal system, genito-urinary system, skin, muscles, bones and joints.

After awhile the idea came to me that all these might be considered as tubes, or were made up of tubes or contained many tubes; and that each tube in the body had a dual nerve supply, i. e., from the sympathetic and the central nervous systems, or if you will, the vegetative and para-vegetative nervous systems.

The Balance of Nature

This idea, taken with the proven fact that the sympathetic or vegetative nervous system is controlled by the ductless glandular system, especially the adrenal or chromaffin system, made the whole thing clear and easy. The embryological studies of C. R. Ide (1) show that adrenal secretion excites the dorsolumbar sympathetic, while the pharmacologic studies of Edmonds and Roth (2) show that adrenin produces its effects by an action on the myoneural junctions of the true sympathetic nerves.

We know there is nothing single in nature and consequently we can readily understand how a tubular structure, with double nerve supply, might fail to function properly because of a lack of balance in its innervation. To me, the mechanism is just the same as the voluntary control of joints. Our anatomy has taught us that each voluntary joint has two antagonistic muscles or groups of muscles. Our physiology has taught us that each muscle is constantly in a state of tone produced by its nerve supply, and, further, that if the nerve supply of one group is lessened, the opposite or antagonistic group is overactive, or hypertonic. Can we not reason by analogy then, that if the sympathetic nerve-tone to a given tube or set of tubes is below par, the central nerve-tone will be above par, or vice versa? In other words, the nerve-tone of the tube is out of balance and consequently there is dysfunction. *Accordingly then, any dysfunction of the sympathetic nervous system is in reality a disturbed balance in the activity of the ductless glandular system, especially the adrenal system.*

The statement has often been made that some practitioners thrive because they have some few *little things* they lay stress on. Is it not true that all big things in life are mode up of *little things?* It is high time that the medical profession gave more attention to these *little things.* They may be met in your office almost every day and if you are not looking for them, they are missed. I know of no field in medicine that requires closer attention to little things than the study of these *little glands.* Here, close observation and minute attention to detail is required. The majority of diagnostic sins are of omission rather than commission. This applies, with especial emphasis, to the elucidation of minor functional disturbances of the ductless glandular system. Our treatment should be directed to the ductless glands and the re-establishment of their normal

balance instead of using measures designed only to stimulate or suppress the activity of the sympathetic nervous system.

THE ROUTINE STUDY OF HYPOADRENIA

This brings me to the real subject of adrenal hypofunction as seen in the every-day practice of medicine. These are not necessarily cases of Addison's disease, but the common conditions which unquestionably have an adrenal basis. Many of the more pronounced cases come complaining, among other things, of weakness; but how are we to know objectively that they are weak? The answer is: Determination of the blood pressure. In the normal, the systolic blood pressure is some 4-10 mm. higher in the standing or erect position than it is in the recumbent position. This is due to the ability of the splanchnic vasomotor mechanism to overcompensate for the hydrostatic effects of gravity.

If we examine the splanchnic veins we find they are devoid of valves, and in this way differ from the veins of the extremities. The strength of the splanchnic veins is dependent upon the quality of their nerve-tone, for any muscle is weak in proportion to the weakness of its nerve-tone. If the nerve-tone is weak, the vein wall is weak and cannot compensate the effects of gravity. Hence, the drop in systolic blood pressure in the erect position as compared to the recumbent position. The splanchnic nerves are controlled by the adrenal system; therefore, weak splanchnic veins means weak splanchnic nerves *and weak adrenals.*

Hill (3) found that anything that weakens the splanchnic vasomotor mechanism interferes with compensation. Sewall (4) has shown that persons in whom there is an excessive gravitation of blood to the lower limbs and splanchnics, are physically weak, nervously unstable and frequently suffer from headache and dizziness in the erect position. Schneider (5) utilizes

postural systolic blood pressure determinations in rating the cardiovascular efficiency of men in air service. Crampton (6) has shown that the systolic pressure falls in the erect position in people weakened by dissipation, overwork, loss of sleep or disease.

The term "neuro-circulatory asthenia" is good as far as it goes, but is it not really hypoadrenia? Any one doing much work with the chronically ill, those that are not sick enough to be in bed, but at the same time are not well enough to efficiently perform their daily duties, is frequently consulted by those in this large class. Their chief complaint is that they do not feel well. In these cases determine the blood pressure, both in the erect and the recumbent positions, and you will be surprised many times at the great difference in the systolic figures. Often I have been confronted by people who say to me, "What is the matter with me, I'm not worth anything. My doctor tells me there is nothing the matter with me, but I know there is." At this point let me appeal for more honesty in our statements to our patients. When we are unable to find trouble in a given patient, let us frankly tell him we find nothing, instead of saying, "There is nothing wrong with you." It is this kind of a patient that, after going the rounds of many physicians, finally becomes disgusted and takes up Eddyism. Later he honestly tells how he was "healed" of some disease that one of thhe many doctors said he had. I distinctly recall a prominent business man who had the "flu" in 1918. He had consulted several doctors about his condition and was advised to take a trip and forget it. He took the trip, but was not benefited. Then his own doctor told him he was lazy. His complaint was about like this: He arose and felt fairly well, breakfasted and went to his work. By noon he was tired, by 3 P. M. he was very tired, and by 6 P. M. he was "all in." After dinner he had no desire for reading, dancing, cards or theater; the only thing

he wanted was to go to bed. This he did by 8.30 or 9 P. M. and then would lie awake until 1 or 2 A. M. before he could go to sleep. Examination revealed no organic disease. Blood pressure systolic erect was 118 mm., recumbent 132, November 13th, 1919. Small doses of adrenal gland with thyroid, spermin and calcium glycerophosphate were given daily. Finally on January 15th, 1920 he called me up and said, "I think you had better give me the once-over, Doctor." When he came in, his systolic blood pressure was 118 mm. in the erect position, and 118 in the recumbent. I remarked that he ought to feel fine. He then said, "If people only knew what those capsules would do for them, they would be fighting for them with guns."

THE ETIOLOGY OF HYPOADRENIA

Let us consider the causes of adrenal hypofunction. In the first place, we must bear in mind the fact that all people are not born with adrenals of the same state of development or functional efficiency. This idea has been worked out experimentally in hogs by Smith (7). He demonstrated that hypofunction of the thyroid in hogs is transmitted to their offspring. May we not then reason that adrenal hypofunction in the mother can be transmitted to her offspring because the thyroid, adrenals and anterior pituitary are all a part of the "adrenal system" as first described by Sajous (8) and later by G. W. Crile (9)?

The inherited cases are to me the chronic cases according to the classification of Emile Sergent (10). In my observation of Russian Jews I have so frequently found evidence of adrenal hypofunction that I have come to believe they all have it. I can readily understand this, for the Jews in Russia for generations have lived in fear of persecution (religious). Darwin (11) maintained long ago that acquired characteristics do become hereditary. Cannon and De La Pas (12) have

shown that emotions such as fear, anger, grief—in fact, any strong emotional excitement—will stimulate the adrenals, and further, that if the stimulus is continued over a period of time, the stimulation gives way and depression follows. This, in fact, applies to all stimulants.

The observations of Kaplan (13) on changes in the formation and position of the teeth in relation to the internal secretory apparatus are indeed interesting and exceedingly helpful in deciding whether a given case is really congenital or only an acquired hypofunction. This, I believe, is vitally necessary in order that we may have some mental concept of the results we expect to attain by organotherapeutic measures. My own observations agree with Kaplan (13), i. e., that blunt, flat upper cuspids, the so-called eyeteeth, are an indication of slow-acting adrenals.

We can get the internal secretory mechanism of the inherited case to working more normally by gland feeding, but the slightest little mishap will throw the whole thing out of balance again, whereas, in the acquired case, our treatment is more prompt and decisive in action, and the results of much longer duration. To lend emphasis let us contrast the following cases:

Mrs. H. J. G., age 27, left Wisconsin in 1908 because of asthma, came to Southern California and asthma disappeared immediately on arrival in Los Angeles. She remained free for three years, when in 1911 an attack of appendicitis occurred. This was followed by a recurrence of the asthma, which continued to December, 1916, when I first saw her. Upon examination, I decided she was suffering from hypocrinism or hypofunction of the pituitary, thyroid, adrenal and ovarian glands. Incidentally, it is interesting to note that her mother, at this time, also showed evidence of pituitary, thyroid and adrenal hypofunction. A combination of pituitary, thyroid, adrenal and ovarian glands was

given, and in thirty days she was free of asthma. She later became pregnant, was delivered under anesthetic at term, and her asthma returned.

The other case was Mrs. J. H. R., age 23, in 1913 had tonsilitis and bronchitis, followed in two weeks by swelling of the feet and ankles, which progressed until the entire body was swollen. Hypothyroidism was diagnosed and one and one half grains of thyroid were given daily. In nineteen days all swelling was gone and albumin and casts had disappeared from urine. Thyroid feeding was stopped. Since that time to date, there has been no return, even though in December, 1918, she had "flu," and also was delivered, under anesthetic, of a normal male child.

SUBACUTE FORMS OF ADRENAL INSUFFICIENCY

Among the subacute cases, we find those following severe illness associated with fever, such as typhoid, influenza, pneumonia, etc., also anesthesia, alcoholism, prolonged worry (which, in fact, is really excessive mental work), focal infections and intoxications. A recent case will serve to illustrate the pronounced adrenal depression which may be caused by worry. Mrs. E. J. W. had been feeling very dizzy and weak for ten days. She complained of her head feeling queer. Systolic blood pressure 100 mm. erect; 128 recumbent. Urine and physical examination negative. Adrenalin chloride solution, 1:1000, ten drops every two and one half hours, was given by month. Next day, July 14th, 1920, erect systolic pressure 110; recumbent 120; July 15th, 1920, erect systolic pressure 116, recumbent 116, and she said she felt fine. I then found out that she thought she had had lues years ago. When the hot weather started she always felt badly, but, heretofore, only for a few days. This ill feeling lasted so long, in spite of catharsis, etc., that she began to worry for fear the old disease was attacking her brain. The

more she worried, the worse she felt. July 15th, 1920, blood and spinal fluid showed negative Wassermann tests. The use of adrenalin, by mouth, served to homostimulate the adrenals and cause the disappearance of all symptoms, before the blood and spinal fluid tests were made.

The effect of focal infection upon the activity of the adrenals is nicely shown in the following case: An old man, age 70, was seen a year ago with Dr. J. R. Perry, of Sherman, California. His blood pressure had been elevated to 196 mm. The doctor found some pus teeth, and advised their removal. This was done, and in two weeks blood pressure fell to 136 mm., systolic, but at the same time he developed "spells" lasting ten to fifteen seconds, during which time he apparently was semiconscious. These spells were always preceded by a chewing movement of the face and jaw muscles. Jacksonian epilepsy was suspected by the attending physician. Systolic blood pressure was now 136 mm. recumbent, *but was only 100 mm. erect.* Sergent's white line was also present. Adrenal hypofunction was my diagnosis. I reasoned that the toxins from the pus teeth had served to irritate and stimulate the adrenals; when these toxins were no longer formed, the excessive stimulation ceased, and there was a depression following. Adrenal gland with thyroid, spermin and calcium were given, with the prompt recovery and return to ranch life in about a month.

SEVERE, ACUTE HYPOADRENIA

In the acute cases there has been either of the following: (a) violent injury, (b) severe hemorrhage, (c) overwhelming infection and intoxication, (d) severe psychic shock or, finally, (e) acute acidosis. I am convinced that many deaths on the operating table are due to acute hypoadrenia, overlooked by the surgeon.

I wish to relate my experience with a case seen with

Dr. B. G. Pinkerton of Los Angeles. In August, 1918, D. R., age 18, one Monday night suddenly developed a fever of 104, which by Tuesday noon subsided to 97 degrees. The boy was delirious continuously from the onset. Tuesday afternoon he began to vomit and have involuntary urination and defecation. One consultant suggested an early tuberculous meningitis; another suggested thrombosis of the lateral sinus, or perhaps a brain abscess. Wednesday morning brought no change. At 9 A. M. Wednesday I saw the patient and found the above condition, with temperature 97 degrees, pulse 140, systolic blood pressure 90 mm. The urine contained both albumin and casts, with plenty of acetone. My diagnosis was acute adrenal exhaustion from the acidosis. Adrenalin-chloride and Kalak water were given by mouth, with a solution of bicarbonate of soda and sodium chloride by rectum, by the Murphy drip method. This regimen soon changed the whole picture. By 5 P. M. the pulse was 110, the systolic pressure 100 mm., with a cessation of the vomiting and lessening of the delirium. The next morning the pulse was 76, systolic pressure was 120, temperature 98.6, and the boy wanted to go home. If that boy had been anesthetized and an operation performed for sinus thrombosis, what chance would he have had for recovery?

THE RELATION OF THE MINERAL METABOLISM

The subject of acidosis is closely allied to demineralization. The adrenals, and, in fact, all the ductless glands, must have the proper amount of the proper mineral salts in the plasma for their perfect functioning. Hypoadrenia, then, also means demineralization, and adrenal feeding will not accomplish much unless we supply these minerals also. Stheeman (14) has shown, using the method of De Waard, that the calcium content of the blood is low in neuroses of the vegetative nervous system, universal asthenia, and tuberculosis;

that the severity of the condition is reflected in the lowness of the blood calcium content and that the calcium content rises as the condition improves.

The treatment of hypoadrenia, whether it be acute, sub-acute or chronic, should be as follows: (1) Support the adrenals by adrenal feeding, instead of whipping them with strychnine; (2) Spare them by removing focal infection and combating intoxication; (3) Supply the mineral salts as found in the blood stream, especially calcium (this can be done by administering the various salts in definite amounts); (4) Insist upon a diet, rich in foods containing bases, with a minimum of foods that produce acids.

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XVI

ORGANOTHERAPY WITH SPECIAL REFERENCE TO THE ADRENALS

By Lillian G. Barker, M.D., Los Angeles, Calif.

The practice of medicine is properly described as an art, "the art of medicine." It is also a science, but our knowledge is so limited that we stand on the very outskirts and view "through a glass darkly" the field to be surveyed and plotted and minutely studied, before we can practice medicine as a science. Only here and there as the mists are dissipated by those in the advance guard of learning, do we discern little islets of truth that we hope may be united into whole continents, giving us eventually a solid foundation of science to support our art.

We cannot, however, wait till we are able to grasp the whole of truth before we care for the sick. We must accept experience as our guide and try to add little by little to the sum of knowledge by interpreting results in the light of the present known facts.

In the November 14, 1919, number of *Science,* Morris E. Leeds, of Philadelphia, discusses the subject of research, with special reference to industrial establishments; but from the standpoint of the true scientist and in a manner equally applicable to any place or condition where chemistry and physics enters into the fundamentals of the processes carried and where serious and sincere study looking toward advancement and development is proposed.

He takes exception to the more recent limitation of the meaning of research, as an uncharted venture into the realm of the unknown and quotes the definitions given in the "Century Dictionary:"

1. Diligent inquiry, examination, or study.
2. Laborious or continued search after facts or principles.
3. Investigation.

And gives the illustrative quotation from Cowper:

> *"He sucks intelligence in every clime*
> *And spreads the honey of his deep research*
> *At his return—a rich repast for me."*

On the other hand, he makes a sharp distinction between a research laboratory and a testing laboratory. "I should not want to see a chemical laboratory, however large and elaborate its equipment or however highly trained its staff might be, called a research laboratory if its sole function happened to be routine analysis and check on the product.

"But every business (or profession) is continually confronted with the need of more information than is possessed by its regular staff . . . and if it is to develop, realizes that it must find new fields," must gather up the work of others and find new relations between the elements of the known and must continually push its thought and processes into the previously untried.

It has been said that the human body contains within itself all the elements needed for the cures of its various diseases. The author must have made this observation in a Pickwickian sense only. At least he could hardly have meant they were present in sufficient amount or suitable proportion at all times.

In the chronically ill, what a wide field of speculative investigation and therapeutic endeavor is presented! Every organ, every gland, every cell is giving out

something to the circulatory fluid, something that is merely a product of its own metabolism, to enable only itself to live; something that may stimulate or enable a distant cell or organ to do its work; something that will in some way modify the metabolic equilibrium upon which health depends.

To the internist there is no department of medicine of more interest and importance. A very little reflection causes wonder at the large number of little children who are not well nourished and robust; at the large number of adults pursuing their usual vocations, but not well. "My neuralgia," "My rheumatism," "My backache"—familiar words, descriptive of conditions more or less cheerfully borne, but borne because the patient knows by experience the difficulty of obtaining relief.

Much of our nomenclature is an index of our ignorance, rather than otherwise. How many of us know what we mean by "neurasthenia," "hysteria," etc? It really seems as if we sometimes call the patient names in our impatience with him for not being or getting well, when our impatience should be with ourselves that we really do not know what is the matter with him, or how to cure him.

The attempt to find a rational basis for treatment by taking into account the simpler facts of physiological chemistry produces astonishment that such things can be. Most of our activities lead to the production of acid in the tissues (arbonic acid). *(Howland Bull, Johns Hopkins Hosp.*, 1916, xxvii, 63), has shown that "this stream of acid . . . with an adult, in the course of the day, is the chemical equivalent of several hundred cubic centimeters of concentrated hydrochloric acid." In addition, there is a large constant elimination of acid, urea and other wastes through the kidneys; there is the detoxicating action of the liver, the circulation of hormones and enzymes, and the many known and

unknown chemical changes necessary to continued life and the maintenance of the stability of the nucleus of the protein molecule which must be preserved in its colloid state during life.

In consideration of these facts the mere maintenance of the circulation assumes a vast importance.

In our routine chemical study, after we have eliminated focal infection, errors in diet, have regulated the rest and exercise, and have narrowed our study to that great field of investigation—the patient him (or her) self, who does not get well, but lingers in that unsatisfactory state that makes the family wish "Aunt Belle would get well or something"—then we may turn to the study of metabolism as affected by the glands of internal excretion, with the hope of doing something helpful.

Even the laity is well aware of the dangers of high blood pressure, but the multitude of ways in which a low pressure may do damage and the great number of patients suffering from this condition, is perhaps underestimated by physicians. Following the epidemic of a year and a half ago, the "flu" left many of its victims weak, exhausted, unable to work, without their accustomed "pep." They poured through the physicians' offices in a steady stream. Most of these people had a blood pressure below normal, and responded promptly either to adrenal or to suitable pluriglandular therapy. This experience has been a great eye-opener to many physicians, and has stimulated investigation in a great variety of conditions in which we may find the same symptoms, and the relief of which goes a long way to turn the tide in favor of healthy metabolism. *It is well worth while to think over the changes attendant upon and conditioned on a lowered blood pressure.*

Such conditions favor a decrease in the cellular oxidation and slow the blood stream, with, therefore, an accumulation of metabolites in the fluids and tissues.

Each cell and each organ is then progressively less able to accomplish its usual work. The heart's contraction is less forcible and its emptying less complete. There is an increase of H-ions in the general circulation with local areas of greater acidosis where the circulation is more sluggish, with the attendant aches and pains so often called "rheumatism." The cause that first got the patient into this condition long since may have been removed, but the patient has never been able to rid himself of the accumulation of metabolites that is keeping him where he is.

Under these conditions, consistent support of the adrenals changes the whole picture. After only a comparatively few doses the patient will say, "Yes, I feel better." His heart beats more strongly, but not so fast; there is a better circulation of blood to and from every part. The nutrition to every cell and organ is better, the excretory products instead of stagnating, are being carreid away, and instead of a vicious circle, we have a beneficent cycle, in which the whole organism profits. It is not the whole story, however, that a better circulation is established, important as that factor is. The presence of a sufficient amount of the internal secretion of the adrenals has a favorable influence on metabolism, increases oxidation, and, therefore, of itself improves the quality of the blood as well as its distribution.

It is doubtless this action and its property of increasing the immune reactions, as well as its circulatory action, that gives to adrenal extract its great value in pneumonia, tuberculosis, typhoid fever and all low asthenic states.

Recently a patient came under observation with a history of pulmonary tuberculosis and pleural effusion some years ago. There had been no evidence of an active pulmonary process for several years. The white blood count was 8.300; the red cells 5,470,000. The

hemoglobin 80 per cent (Talquist). The urine showed no albumin, sugar, or acetone. There was urobilinogen and urobilin and an acid elimination of 230 degrees. There were no pus cells or casts. She had been operated on for appendicitis, and had had several suspicious teeth extracted. No organic disease could be found, but for a long time she had felt very weak, spoke in an all-gone tone of voice, complained of attacks of dizziness and was convinced there was something very wrong with her. Her blood pressure was found to be only 64 mm. diastolic and 98 mm. systolic! On the strength of this she was temporarily put on adrenalin, by mouth, followed by certain pluriglandular capsules. A few days later the sparkle in her eyes and the animation of voice and gesture told the story.

Another patient gave a history of headaches from childhood. She had spent much money in the attempt to obtain relief. Among other things, had had eight Wassermann tests! Her low white count and low blood pressure suggested the advisability of supportive glandular therapy. In the course of a few weeks she was much relieved and declared nothing had ever done her so much good.

Such histories could be continued almost indefinitely; and many conditions in which the same therapy is indicated readily suggest themselves.

In this connection a report of Dr. Cazamin, Chief Medical Officer of the "Jean-Bart," is interesting. He made a special study of 50 cases of seasickness from the standpoint of adrenal function. He found that there is at first a stimulation of the sympathetics with increased production of adrenalin, with a resulting higher blood pressure, tachycardia, inversion of the oculocardiac reflex and dilatation of the pupils.

The symptoms suggest excessive production of adrenin at first. Then the adrenals soon become exhausted and the blood pressure drops. During the first phase

there is a sympatheticotonic paroxysm. During the second phase the clinical and pathogenic phenomena are very like those of shock.

Cazamin remarks that people inclined to sympatheticotony are peculiarly predisposed to seasickness, while the vagotonic escape.

In the second phase, adrenalin, by mouth (the equivalent of 6 mg. in three doses at half-hour intervals), gives good results.

During the stage of hyperadrenia he has obtained absolutely constant, excellent results, both in prevention and in curing the seasickness, from hypodermic injections of neutral sulphate of atropin in doses varying from 0.001 to 0.002 gms.

As we know of no dependable drug that will check the functioning of the sympathetic nervous system, the next best thing is to act on the antagonistic nervous system. By influencing the vagus in this way with atropin, we thus indirectly control the sympathetic. The question whether adrenalin or atropin is called for is easily answered by the oculocardiac reflex. His experience indicates that with one or the other of these drugs we can ward off and cure practically every case of seasickness.

Another interesting class of cases comes to mind. Many times the form of paroxysmal tachycardia, which depends upon an imbalance between the thyroid and adrenals, with a moderate excess of thyroid secretion, may yield to a few doses of adrenalin in a very gratifying way. There are few services for which the patient is more grateful than to have the pounding heart quieted down. The same remedy is almost a specific for the insomnia associated with this form of endocrine disturbance. Recognition of this factor will save hours of sleep to the patient.

The manifold uses and great therapeutic value of adrenal extracts are, perhaps, more readily understood

and credited if we remember the common blastodermic origin of the adrenals and the sympathetic nervous system, and how both seem to work together to keep the machinery going, while we go on with our work and play without troubling ourselves as to details, unless one finds difficulty with its job and the functions which usually are going on so quietly, rise to consciousness, when a little regulation of the right kind may make all right again.

We have always to keep in mind that life is consistent only with a certain chemical equilibrium and the retrograde changes that appear when the circulation is depressed, to think of innumerable instances in which this therapy is applicable.

Until we are able to diagnose slight endocrine dysfunction more accurately and to determine the resulting pathology, we shall not be able to treat these cases other than empirically, but a beginning is already being made to place this matter on an unassailable, scientific basis.

The work of Georgine Luden is interesting; her experimental work tending to show the metabolic upset attendant on the climacteric glandular changes is a factor that allows of the excessive cell proliferation in malignancy. She argues that there is an increase of cholesterin in the blood and that this favors excessive cell proliferation and malignancy. The cholesterin metabolism and its elimination are regulated by the adrenals, liver, spleen, ovary and corpus luteum in order of importance. Incidentally, her argument goes to show that the accumulation of fat at that time is a factor of safety under the conditions, serving as a storehouse for the surplus cholesterin, and that it is not the adiposity that should be treated, but rather the glands of internal secretion, whose faulty working allows the accumulation of abnormal amounts of cholesterin in the blood and tissues.

XVII

INVESTIGATIONS OF SOME BIOLOGICAL EFFECTS OF ADRENALIN

By Dr. Leon Binet, Paris, France

The work that we have the honor of addressing to "THE HARROWER LABORATORY" is the result not of documents sought for in medical literature, but of personal investigation, made in various laboratories with the assistance or under the direction of our masters, Professors Ch. Achard, H. Richet and H. Roger. These inquiries are related to:

1. The action of adrenalin on carbohydrate metabolism.
2. The action on the heart.
3. The action on shiver (tremor).
4. Its action in anesthesia.
5. Its action on tetany.

The bibliography which follows them is a complete list of the publications in which some of these inquiries have been expounded.

I

The Action of Adrenalin on Carbohydrate Metabolism

It is now known, since the publication of the work of Blum, Zuelzer and Metzger, that the injection of adrenalin, either under the skin or into the veins brings about glycosuria, and it is proved that this glycosuria is connected with an increase of sugar in the blood. This

adrenalin hyperglycemia is accompanied, as shown by Achard and Desbouis, by a deficient glycolysis, that is, a lessening of the capacity of the tissues to burn and fix the glucose of the blood.

With the assistance of Ch. Achard and A. Ribot, we have taken up the question of the action of adrenalin upon the consumption of glucose, and for that purpose we have studied, in the dog, the characters of the hyperglycemia provoked by an injection of glucose and, these characters being known, the variations of this hyperglycemia when a certain quantity of adrenalin is injected with the sugar. In every experiment, glucose was injected in aqueous solution (35 grams to the litre) and at the beginning of the experiments was withdrawn before the injection and then every ten minutes following the injection. Our method has been done following the procedure of A. Epstein, which allows volume of blood in a great proportion and, therefore, without altering the quantity of sugar in the blood. The *duration* of the hyperglycemia, provoked by the injection of glucose, seemed to us a most important point, indicating the capacity of the organism to fix this sugar. In a series of healthy dogs we obtained the following results:

1. A dog, weighing 12 Kg., was injected with 12 grams of glucose; after 2 minutes the quantity of sugar in the blood went from 1 gm. per litre, to 3.10 gm.; the glycemia came back to the starting point after 40 minutes.

2. A dog, weighing 19 Kg., was injected with 12 gm. of glucose; after 2 minutes the sugar went from 0.9 gm., to 2.65 gm. and came down to 0.90 gm., 30 minutes later.

3. A dog, weighing 19 Kg., was injected with 10 gm. glucose: the quantity of sugar went from 1.05 gm., to 2.85 gm., after 2 minutes and came back to the starting point in 20 minutes.

4. A dog, weighing 15 Kg., was injected with 3.5 gm. glucose: the sugar went, after 2 minutes, from 0.95 gm., up to 1.40 gm., and was normal 20 minutes after.

5. A dog, weighing 33 Kg., was injected with 7 gm. glucose: 2 minutes after the quantity increased from 1.15 gm., to 1.95 gm., and back to 1.15 gm., after 10 minutes.

From those experiments, selected from several others, we may conclude that the degree and duration of the hyperglycemia provoked by the injection of glucose evidently are in proportion to the amount of glucose injected. The duration of that phenomenon gives very clear indications and we can admit that with half a gram of glucose per kilogram, the hyperglycemia lasts about 20 minutes and with one gram per kilogram it lasts about 40 minutes. We might wonder what becomes of the injected glucose: Part is eliminated through the kidneys, as it is shown by a glycosuria following the hyperglycemia; the rest is either fixed or burned up. In fact, the analysis of the gases in the veinous blood or of those expired, shows the quick combustion of the assimilable sugar, if everything is normal.

The comparative study of the quantity of sugar after the injection of assimilable glucose and, on the other hand, after the injection of unassimilable lactose, clearly proves the part of the destruction and fixation of the sugar during the phenomenon.

A dog, weighing 22 Kg., was injected with 15 gm. of glucose: hyperglycemia disappeared 45 minutes after. Some days later he was injected with 15 gm. of lactose; the quantity of sugar doubled 45 minutes after: 0.78 gm., at the beginning, and 1.95 gm., after 45 minutes.

What becomes of a hyperglycemia when adrenalin is injected with the glucose? We have studied this, considering, in each experiment, the effect of glucose alone,

then the effect of adrenalin, and lastly, the effect of both together.

A dog, weighing 15 Kg., was injected with 3.5 gm. of glucose, 2 days after, with 1 mgm. of adrenalin, and lastly, 2 days later, with 3.5 gm. of glucose, plus 1 mgm. of adrenalin.

Quantity of sugar in blood after an injection of:

	3, 5 gm. glucose.	1 mg. adrenalin.	3, 5 gm. glucose + 1 mg. of adrenalin.
Before	0, 95	0, 95	0, 95
2 min. after	1, 40	——	1, 70
10 min. after	1, 10	1, 40	2, 10
20 min. after	1,	1, 20	1, 70
40 min. after	....	0, 92	1, 30
1 hr. 20 min. after	....	....	1, 10
2 hrs. after	....	....	0, 95

This shows that the addition of adrenalin to glucose brings an increase of sugar greater than the sum of the increases brought by adrenalin alone and glucose alone. In addition, this hyperglycemia lasts longer since it lasts after an hour and twenty minutes. It is as if the organism, under the influence of adrenalin, could no longer fix and burn up the sugar: its power of glycolysis seems absent.

These experiments seem to us to develop some practical applications; in therapeutics it seems to us that there is an incompatibility between glucose and adrenalin: the serum containing both glucose and adrenalin seems not to be used.

But how are the conditions of hyperglycemia and incompentency of glycolysis produced? Numerous opinions have been expressed about this. With Ch. Achard and A. Ribot, we have tried to solve this problem by studying the effect of an injection of adrenalin after the extirpation of the pancreas. This is a problem so much the more interesting as the relations between the adrenal glands and the pancreas have been recently sought

for (R. Pemberton & J. E. Sweet—E. Gley—Graham, Lusk & Riche—F. C. Mann & Della Drips).

1. Dog weighing 10 Kg. Injection of 1 mg. of adrenalin.

	Normal Dog.	Sugar in blood after pancreas was out
Before	0,65	3,20
10 min. after	0,80	3
20 min. after	0,60	3,20

2. Dog weighing 10 Kg., having its pancreas removed 6 days previously. Injection of 2 mg. of adrenalin into the saphenous vein; the quantity of sugar, within the following half hour, remains at 3 gm. per litre.

	Sugar in blood.
Before	3 gm.
After 2 mg. of adrenalin	3 gm.
10 minutes after	3 gm.
20 minutes after	3 gm.
30 minutes after	3 gm.

Such conditions do not exist if the extirpation of the pancreas is not complete, and a dog, which had had the pancreas removed 13 days before, but still had a stump of pancreas left, as was shown by the autopsy, showed an adrenalin hyperglycemia:

Dog weighing 9 Kg., had its pancreas out on May 21, was injected June 4, with 2 mg. of adrenalin.

	Sugar in blood.
Before	1
15 minutes after	1,30
30 minutes after	1,50

The animal was killed and a stump of pancreas about the size of a pigeon's egg was found against the duodenum. These experiments show that adrenalin hyperglycemia is not produced after the extirpation of the pancreas. Finally, it is as if adrenalin injected into a dog *prevented the action of the glycolytic ferment from the pancreas, its action on glucose seems indirect and is suppressed by the previous suppression of that ferment by the extirpation of the pancreas.*

II

THE ACTION OF ADRENALIN ON THE HEART AND VEINS

The temporary hypertension produced by an injection of adrenalin is a very well-known phenomenon. It seemed to us of interest to consider the disorder brought by large doses of adrenalin, which would produce an exaggerated hypertension and might even cause the death of an animal.

That edema of the lungs is caused by an injection of adrenalin is fairly well known; but in addition to this reaction in the pulmonary circulation, we have observed a more frequent manifestation in the pericardium.

First Experiment—A dog weighing 7 Kg., was injected with 5 mg. of adrenalin, then, 30 minutes after, with 3 mg. and 1 hour later with 1 mg. of the same substance. The animal was killed an hour and a half after the beginning of the experiment. Autopsy showed no pleuropulmonary injury, but the heart showed in the myocardium some signs of hemorrhage in the left part only (right part normal). Those hemorrhages of the myocardium were accompanied by a slight, rosy discharge, containing 56 g. of albumin per litre and some heminfiltration of the pericardium.

Second Experiment—A dog, weighing 7 Kg., was injected with 7 mg. of adrenalin within an hour; the animal was killed and hemorrhages in the myocardium were found in the right as well as in the left part of the heart with a discharge of the pericardium of 6 mils. Lungs as usual.

Third Experiment—A dog, weighing 12 Kg., was injected at 4:45 with 5 mg. of adrenalin, and at 5 with 6 mg. At 6 o'clock the animal was killed by puncture of the bulb and 13 mils. of a slightly pink liquid were found in the pericardium. The myocardium showed

hemorrhages, especially near the left ventricle. Lungs as usual.

Fourth Experiment—A dog, weighing 8 Kg., was injected within an hour with 10 mg. of adrenalin. One hour and a half after the beginning of the experiment the animal was killed and a large amount of fluid in the pericardium, with several hemorrhages in the myocardium, were found. Lungs as usual.

In these experiments the lungs remained uninfluenced, but in some others the opposite is the case; and on the other hand, the pericardium is not altered.

Fifth Experiment—A dog, weighing 7 Kg., was injected with 5 mg. of adrenalin. The next day the animal died and at the autopsy edema of the lungs, with a pink liquid in the pleural cavity, were found. The pericardium was free from this fluid, but there were some signs of hemorrhage in the myocardium on the right (ventricle and auricula), and even one was found on the valves of the pulmonary artery. The left part of the heart was normal.

From those experiments we may conclude that:

1. There is an acute exudate into the pericardium after certain injections of adrenalin.

2. That liquid is slightly hemorrhagic, yet having a composition different from that of the serum.

3. That a pericarditis may occur, which is accompanied by injuries of the myocardium, especially in connection with hemorrhages of the left part of the heart.

4. It does not happen when the animal has a marked edema of the lungs, as if there were two fragile parts: *one in the lungs, which is shown by the swelling of the capillary vessels, the other in the pericardium, which is shown by the swelling of the pericardium.*

In cases of hypertension there may be injuries in the pericardium of such a character that adrenalin is not to be used in pericarditis and also in edema of the lungs.

III

THE ACTION OF ADRENALIN ON SHIVER

Adrenalin has an action on certain nervous manifestations, particularly upon shiver. The experiments of Professor Ch. Richet have shown that a chlorilized dog, having a temperature of 34° C., was taken at first with a shiver on inspiration, then when both inspiring and expiring a violent shivering occurred so as to increase inspiration and expiration evidently in order to raise the temperature.

Our experiments have shown that if an animal in such a plight was injected with 1 mg. of adrenalin, its shivering was stopped instantly, as well as the respiration. If only ½ mg. were injected, the respiration might not be altered, but the shivering would be stopped. It seems that the center, which controls shivering, is more sensitive to adrenalin than the center which controls respiration.

Adrenalin momentarily stops the thermic shiver; it also stops the reflex shiver observed on an animal that is awake. Lastly, it prevents the development of the shivering caused by the injection into the veins of certain substances as sugars.

If some glucose serum is injected into a non-anesthetized dog, immediately a violent and long continued fit of shivering is produced; if, on the contrary, serum containing both glucose and adrenalin is injected, the shiver is not produced. *Thus adrenalin seems to us an excellent remedy for the shivering, whatever may be its cause.*

IV

THE ACTION OF ADRENALIN IN ANESTHESIA

Experimentalists do not fail to be struck with the dejected look of the animal which, when awake, is in-

jected with adrenalin. The dog which, but a moment ago, was barking and lively, becomes quiet and silent. That fact must be remembered, and J. Gautrelet praises the use of adrenalin in anesthesia of animals by means of chloralose. His experiments show that the period of the excitement before anesthesia, caused by chloralose, is suppressed if adrenalin is injected previously. In man, Pierre Delbet, Herrenschmidt, Beauvy and Carlo-Oliva have considered the action of chloroform on the adrenal glands.

It seemed worthy of interest to us to study the effect of adrenalin upon the resistance of guinea pigs to chloroform. Under a glass bell, containing about 30 litres, two guinea pigs were set. They weighed the same; the one was a control; the other was injected under the skin with 2/10 mg. of adrenalin; chloroform vapor could be blown through the receiver. Anesthesia lasted from 10 to 25 minutes, then the animals were removed. The animals were under observation immediately after and on the following days; but often this anesthesia was enough to cause the death of one of the animals.

The results of our experiments show:

First, in 10 controls:

One animal recovered.

Nine animals died, of which 8 were under the bell during anesthesia, and 1 dying after the animal had been removed and was no longer under chloroform.

Second—In 10 guinea pigs having been injected with 2/10 mg. of adrenalin:

Two animals died (one immediately, the other some days after).

Eight animals recovered.

Such figures should suffice to prove the value of adrenalin as a preventive of the shock caused by chloroform.

V

THE ACTION OF ADRENALIN ON TETANY

We know that the dog which has been deprived of the parathyroid has motor troubles, shown by attacks of tetany; and respiratory troubles, shown by periods of polypnea—these troubles coming on as a result of various causes. Our experiments have shown us that the injection of 0.5 mg., or 1 mg. of adrenalin in a dog deprived of the parathyroid is followed,—

First, by an attack of tetany, beginning some seconds after the injection, reaching its maximum half a minute after and composed of convulsions and muscular contractions;

Second, by a period of polypnea, following the tetany, connected with an increase in the bodily temperature (40°4), as well as with no increase at all.

Such experiments show that *adrenalin must not be used in cases of tetany.*

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XVIII

ENDOCRINOLOGY IN PEDIATRICS

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It is the object of this essay to simplify the study of the endocrine disorders as they occur during infancy, childhood and early youth. In order to accomplish this one first must have a clear understanding of the physiological activity and relations of the glands of internal secretion. The effects produced through either hypofunction or hyperfunction of these glands, or both, cause a great many metabolic and growth disturbances early in life. It is, indeed, important to recognize these changes early—long before puberty, before the pathological changes in the organism become fixed and difficult to treat—in order to get beneficial results. To succeed in clearing various obscure points in the following chapters I will describe in brief detail the early and late pathological states produced by pluriglandular disturbances in the organism. The object of this arrangement is to enable the reader to compare these findings and thereby learn how to recognize the changes as they occur in infancy, childhood and early youth so that early treatment can be administered with the hope for good results in remedying the curable endocrinopathies and preventing adult dyscrinisms whenever possible.

**The writer of this essay received the fourth prize of $50.00*

HISTORICAL SUMMARY

Although in the fifteenth century Paracelsus described his observations of cases of cretinism and goitre, yet the entire subject remained dormant until Johannes Muller and Ruysch, in 1844, showed that the blood received secretions from certain ductless glands. In 1849 Berthold, of Göttingen, experimented on animals to ascertain the true nature of the ductless glands. Leydig, in 1850, described his work with the gonads; the intertubular connective tissue cells of the testes still bear his name—the "interstitial cells of Leydig." The term "internal secretion" was first used by Claude Bernard in 1855, when he described the glycogenic function of the liver as its *"sècrétion intérne."* The real beginning of ductless gland research dates back to 1855, when Thomas Addison described the syndrome caused by the changes in the adrenal glands. Starling, of University College, London, gave us the term "hormone"—initiators or arousers of function—in 1902 in connection with his epoch-making work with secretin, the duodenal internal secretion. Later, Sir Edward Schaefer, of Edinburgh, distinguishes the hormones, which promote activities of another ductless gland, from the chalones, which have an inhibitory influence.

Since Brown-Séquard's first efforts to utilize testicular extracts for therapeutic purposes and Berthold's experiments on capons, in 1889, to determine the existence of internal secretions in the sex glands, many theories have been advanced to explain the individual functions of the ductless glands. It can be realized today how wide the field of activity is regarding ductless gland work—its therapy, physiological relation and activity—when the literature upon the subject is consulted. Within the past ten years endocrinology has taken on definite form as a real science, and is fast becoming one of the most important branches of med-

icine as well as therapeutics at present engaging such prominent men as Barker, Sajous, Cannon, Harrower, Kinnicut, Pottenger, Borchardt, Sergent, Perrier and many others in its work.

GENERAL CONSIDERATIONS

The successful organotherapy of the various endocrinopathies which are either fundamental or incidental in children's disorders involves a broad understanding and a knowledge of details, greater, perhaps, than in any other line of medical work. Not infrequently it is the absence of such knowledge on the part of medical men which explains a great deal of the therapeutic doubt and skepticism which exist at the present time. Therapeutic nihilism in ductless gland therapy as far as pediatrics is concerned, and also any other branch of medicine, invariably means gross ignorance and incompetence. Without a doubt, a great deal of judgment must be used in the study of these cases as well as in the selection of these remedies.

I will now consider the most important of the endocrinopathies that exist in the disorders of children, such as nutritional disorders; anomalies of growth and morphogenesis; anomalies of the sex glands and reproductive organs; and certain of the nervous and muscular disturbances.

NUTRITIONAL DISTURBANCES

There exists an intimate relationship between the internal secretions and the growing organism. Observations upon the growth and development during infancy and childhood are of utmost importance. Only through such means are many diseases detected in their incipiency. I have divided the various nutritional disorders into definite types, each being characteristic of its associated dyscrinism.

Type 1. Marasmic cases seen in infancy have been shown to be associated with an abnormally early atrophy of the thymus gland. In treating these cases all attempts at drugs, wet-nursing and artificial infant-feeding often failed. Within the past three years I have been giving thymus gland with small doses (gr. 1/8) of thyroid with excellent results. This treatment I keep up for several months, with intervals of ten days every six weeks. In the milder forms of infantile atrophy, resembling rickets, the little patients fare better with a pluriglandular combination of the above with lymphatic gland, such treatment favoring the mineral metabolism and lymphatic circulation as well as the cellular oxidation, which it will be recalled, is largely controlled by the thyroid gland.

Type 2. Rachitis, or impaired nutrition, with alterations in the growing bones of children, sometimes latent up to the ninth or twelfth month, is due to calcium, phosphorous or mineral metabolic disturbances. Associated with this we have sluggish lymphatic activity, retention of the cellular toxins and often a resultant hypoadrenia. With this frequently one finds an associated hypothyroidism and dyspituitarism as evidenced by the low blood pressure, tendency to dwarfism, muscular and arthritic pains, sluggish mentality, soft and flabby tissues—especially the skin, which sometimes resembles myxedema; muscular weakness and various abnormal changes of the bones and cartilage with lack of calcium deposition. In these cases it is well to note also the close relationship of rickets to hypoparathyroidism since these children often suffer from infantile convulsions, tetany and laryngysmus stridulus, which class of disorders are akin to the convulsive type of difficulties which have been definitely connected with parathyroid insufficiency. As a result of these conditions in these cases we sometimes find an enlarged spleen, liver and lympathics. In such cases I get excel-

lent results from long-continued use of small doses of thyroid with or without other synergistic endocrine remedies.

Type 3. The adrenal type of malnutrition includes those emaciated, pale, tired-out children, who always have circulatory inefficiency with cold hands and feet. Their muscles are flabby, blood pressure is low, the appetite carpricious, and mentality sluggish. Indolence and disinterestedness is usual, and the generally low resistance, marked asthenia and poor elimination of waste products ofttimes is associated with a nephritis. In this class I get the best results from applying the principles of adrenal support so thoroughly emphasized by Harrower, plus, of course, proper care of the emunctories, well-enforced rest, and good food.

Type 4. Certain children, of what might be called a hyperadrenal type, show signs of sympathetic stimulation, rapid heart action, unstable digestion, with frequent gastric disturbances, and dilated pupils. The skin is soft, moist, and there is a tendency to hypertrichosis. They are often emaciated and anemic, but many of them tend toward an excessive development of the body and ossification of the bones, and they appear tall, thin, and delicate. Often they are especially predisposed to infection. In these cases anti-adrenal measures give the best results, and since the pancreas opposes the adrenals, combinations containing this preparation are sometimes marvelous in their effects.

Type 5. In many cases of so-called chronic constipation in children, a more careful examination will reveal other symptoms, which point to a condition of hypothyroidism. These symptoms include a tendency to obesity, laziness, fatigue, somnolence and anorexia. There is a retardation of certain developmental processes as dentition, walking and speech. Muscular and arthritic pains are usual, and frontal and occipital headache is common. Apathy, indolence, depression

and mental retardation make a picture that may be indeed pathetic. Not infrequently there is also an imperfect development of the sexual organs and functions. Thyroid therapy gives excellent results in such cases, though the treatment must be long-continued and the dose increased from time to time, carefully watching for symptoms of thyrotoxicosis, such as tachycardia, insomnia, headache, pain in the back and limbs, trembling and prostration—at the slightest evidence of which the dose should be promptly reduced.

Type 6. Malnutrition, accompanied by hyperthyroidism, occurs usually in older children, beyond puberty, and the difficulties may begin at that time. Exophthalmos may be associated with this condition, but it is rare. These individuals usually are tall, thin, and high-strung. They appear anemic and manifest many of the symptoms that one finds with hyperadrenia (Type 4). They are very temperamental and excitable and some of them exhibit a tendency towards precocity or even genius. The influence of hypercrinism upon the vegetative system brings about the symptom-complex known as sympatheticotonus. Cardiovascular disturbances are the rule, tachycardia is common, and frequently bounding arterial pulsations in different parts of the body are noted on examination and are sometimes an annoyance to the patient. The skin is moist and periodical vasodilation occurs very easily. These individuals blush easily. Hypertrichosis is occasionally found, and it is remarkable how frequently urticaria or similar dermatoses are found. The large, brilliant, oftimes slightly protruding eyes are rarely associated with exophthalmos and conditions of this kind may be easily mistaken for multiple sclerosis. They also may suffer from such neuropsychic conditions as migraine, neuritis and mental disorders. The use of the adrenal sympathetic sedative formula, originated by André Crotti of Columbus (pancreas, adrenal, pituitary, and

ovary), has given me quite the best results in these cases. Lymphatic gland therapy sometimes is an advantage and thyroidectin with quinine hydrobromate are also synergistic. In those who suffer from marked thyrotoxicosis with exophthalmos and degenerative changes of the heart, I advise surgery. [Thyroid surgery must be avoided wherever possible in children and youths.—H. R. H.]

Type 7. A certain class suffer from irregular constitutional symptoms which are connected with disturbed elimination. There is a tendency towards so-called gouty conditions and the uric acid diathesis. Joint conditions are common, and deposits of sodium biurate in or about the joints may bring about serious deformities. With this may be found polyuria and nutritional disorders, which point to a functional disturbance of the pituitary body, which is supposed to control the metabolism of the purin bodies, and has been definitely connected with the etiology of diabetes insipidus. A close study of these children occasionally will disclose slight evidences of the changes in the features expected in acromegaly. The treatment of these cases involves the use of thyroid and pituitary extracts, and the results are sometimes very good, especially when the diet is regulated in regard to its purin content and special efforts are directed to the regulation of the emunctories.

Type 8. The lymphatic type. Many children suffer from nutritional disorders with or without anemia, in which the liver, spleen, and lymphatic glands are definitely involved. These children appear undernourished, underfed and phlegmatic. They often puff up at the least exertion and breathe like asthmatics; they may indeed have well-defined attacks of asthma. They are particularly subject to blood and lymphatic dyscrasias. They bleed easily, may show petechial areas in different parts of the body or give a history of a disturbed coag-

ulating power. The blood findings lean to both lymphocytosis and leukemia, although they need not necessarily be classed in this latter category. Such cases, however, frequently have enlarged lymphatic glands, especially in the neck, and adenoids and enlarged tonsils are the rule. Many times the adenoids recur one or more times after operation. Their susceptibility to infections is particularly great, and decayed and malformed teeth are practically always present. Such children seem to be predisposed to tetany and convulsive conditions, and later on do not develop sexually as they should. The disturbed endocrine function in these cases, to my mind, is connected with the thymus, thyroparathyroid combination and the sex glands, as well as the closely related hemopoietic organs. They do well on a pluriglandular organotherapy definitely directed at the most obvious phases of their symptomatology, and I have been in the habit of using preparations of lymphatic glands, thymus, and the interstitial cells of Leydig and sometimes spleen extract, with satisfactory results.

Type 9. Malnutrition, associated with anemia and blood dyscrasias, such as purpura, hemophilia and scurvy are due to faulty mineral metabolism, reduced alkalinity of the blood, changes in the viscosity of the blood and disturbances of the hemopoietic organs and lymphatics. In these cases the thyroid, parathyroids, thymus, lymphatics, spleen, liver and bone medulla are mainly affected. Hemoglobin is valuable, especially when combined with the indicated endocrine remedies. Lymphatic extract often gives good results in this type of cases.

ANOMALIES OF GROWTH AND MORPHOGENESIS

Disturbances of the internal secretions are responsible for the anomalies of growth and morphogenesis. The difficulty in diagnosis, as well as treatment, lies in

one's ability to recognize these abnormalities early, when our efforts are more likely to be effective. If, when making the physical examination of the child, we will note the normal anthropometric data, the normal mental status, the tonicity of the muscles, the condition of the skin, the size and integrity of the sex organs, the condition of the special sense organs and the physical signs dependent upon sympathetic, parasympathetic and vasculomotor control, we will discern much valuable information regarding the early stages of pluriglandular dysfunction.

To cite an instance: E. S., five years old, was brought to my clinic at the Lenox Hill Hospital, complaining of chronic constipation and headache. The mother wandered with her from doctor to doctor, to various consultants and institutions, and was told that the child had a nervous disorder, due to autointoxication from chronic constipation. By careful examination of the child I found that she had a dry myxedematous skin, flabby muscles, muffled speech, stunted growth, retarded walking, dentition and mentality. This case was typical of hypothyroidism. She improved under thyroid treatment, her constipation disappeared without laxatives and her general condition was very much better. I can recall many similar examples, too numerous to report in this limited paper.

GROWTH DYSTROPHIES

In dwarfs, the abnormal physical signs may show themselves early. As a rule, we find undeveloped members of the body, such as one upper or lower extremity, one-half of the face, etc. Parrot, Porak and Marie have reported many such cases. Kaufman applied the term "chondrodystrophy" to the cases he reported. These conditions are caused by thymus and pituitary dysfunctions as evidenced by the defective and unequal cartilagenous and bone growth. In my case of dwarf-

ism in twins I reported recently, I began to treat them, by suggestion of Dr. Harrower, with thymus, thyroid and anterior pituitary extracts, and there is evident improvement in their general growth and intelligence.

In the treatment of infantalism, due to cretinism, pancreatic insufficiency (Bramwell type), chronic diarrhea and syphilis, we get good results from the specific treatment of the respective underlying causes. In acromegaly we may, at times, observe the abnormal processes of bone growth, chiefly of the face and extremities in young children. This is, however, not conspicuous until after puberty. Gigantism occurs earlier. The Froehlich, Burnier and the Cushing types include all the possible acromegalic or dyspituitary changes. The symptom-complex here consists of skeletal overgrowth, a highly sensitive sympathetic system, excessive sexual development—often to precocity in children—excessive hair growth and distribution, and reduced carbohydrate tolerance. Hyperpituitaric individuals are irritable, bright but distrustful, petulant, indecisive, abusive and unreliable. This condition is often associated with syphilis and, therefore, a Wassermann test should be made in every case. I have gotten good results from the use of various pluriglandular formulas.

ANOMALIES OF THE SEX GLANDS AND REPRODUCTIVE ORGANS

Gonad disturbances are associated with dysfunction of any or all of the internal secretary glands. There seems to exist a reciprocal relation between the thymus and the reproductive glands. Atrophy of one causes hypertrophy of the others. (Henderson.) Experimental evidence seems to point to the fact that the formation of the corpora lutea leads to the development of the mammae, secretion of milk and hyperplasia of the uterus. Its chief function is the formation of the

uterine decidua and the fixation of the embryo. Because of these, I usually employ this gland in treating tardy menstruation, and when I suspect by reason of undue adiposity, delayed menses and small external genitals, the condition of atrophy of the uterus or ovaries in young girls.

In *hypogonadism* the children increase in weight, the skeletal bones are large, and the head is small. There is a tendency to glycosuria and adiposity. Again, in others we may see an essential infantilism with defective development of the genitals and secondary sexual characteristics. In the male the development of the genital organs is controlled by the interstitial cells of Leydig, but are secondarily affected by the pituitary, thyroid, pineal, thymus and the adrenal cortex. The treatment of these cases depends upon the presence of the other physical signs associated with the hypogonadism. I have used various forms of organotherapy in these cases with much success.

In *hypergonadism* there is an enormous overdevelopment of the body, excessive growth of hair and distribution, and the libido-sexualis is developed as in adults. Van Haller reports a case in a girl of this type, who was impregnated at 8 years of age, shortly after this abnormal growth showed itself, and who died at the age of 75 years. The intelligence is well-developed, but childish, the voice is prematurely changed and erections and ejaculations have been noted even in infancy. In these cases the excessive development of the genitals precedes the overdevelopment of the body. As a result of this premature closure of the epiphyses is brought about and these children, although too big for their age, cannot become giants. They are, as a rule, sexual perverts. Malignant disease of the ovaries or testicles may give rise to this condition. In females we get overdevelopment of the breasts, uterus and vulva, menstruata praecox, excessive body-growth, with prema-

ture ossification of bone centers, dentition and epiphyseal closure. In these cases we have an abnormally early atrophy of the thymus and parathyroids with hypersecretion of the pituitary, thyroid, adrenals and pineal glands. It is interesting to note that in older children the symptoms of hypernephroma also manifest themselves by overdevelopment of the sexual sphere. They approach the masculine type and often grow beards and mustaches. In pseudohermaphroditism of the feminine type there is found bilateral hypertrophy of the adrenal cortex. The enlargement of the adrenal cortex has been noted in animals during breeding, pregnancy and after castration. This, together with the fact that the cortex is of small size in deficient sexual development, are additional evidences of the association of the adrenal cortex with sex characteristics.

Eunuchoidism is an acquired disorder of the interstitial cells of Leydig. Those cases manifesting this disturbance are quite similar in functional capacity to a castrate, but without the absence of the testicles. This condition is usually associated with dyspituitarism, hypothyroidism and hypoadrenia. Undescended testicle is not due to adhesions, as formerly thought, but to some pathological condition or abnormal lining of the Leydig cells. When organotherapy alone is insufficient, early operation is indicated in order to avoid untoward complications, such as cancer of the undescended testicle, strangulation of the cord, if tortioned by axial rotation, and possible gangrene of the involved structures.

NERVOUS AND MUSCULAR DISTURBANCES

When there is a suppression or stagnation of the secretions of any or all of the ductless glands we may have a state of degeneration of both mind and body. We may have amentia ranging from the backwardness of the imbecile to profound idiocy, including the amaurotic, moral and microcephalic forms. The hebephrenic

phenomena of melancholic type, incident upon puberty, are quite noticeable among school girls. Small and long-continued doses of thyroid improve the mental condition of these children. After a period of two years of treatment they enjoy a fair degree of mental health and activity.

In hyperthyroidism, on the other hand, we may find the active manias and neurasthenias, sympatheticotonic and vagotonic irritability, while, as a result of dyspituitarism we see sexual infantilism, apathy, backwardness, lack of ambition and inability to do ordinary work. In the former, I get good results from Crotti's pancreas combination, thyroidectin and quinine hydrobromide and in the latter with pituitary preparations.

In those suffering from ovarian and testicular disturbances we get sexual perversion, mental disorders, erotomania and active or depressed mania. The menstrual periods have special bearing upon the metabolism and mental forces. In these disorders they improve on organotherapy, such treatment being instituted according to the predominating symptoms in the individual case. The study and practice of the treatment of psychiatry of insane cases in institutions and its relation to internal secretions and metabolism deserves a great deal of attention. Much can be done along these lines for children before puberty, which will help to prevent these psychic disorders later on. Dr. Sajous found that 65 per cent of all idiots are deprived of their thymus before six years of age.

Hyperparathyroidism is believed to be a cause of myasthenia paralytica (Chvostek) and of the rarer condition known as myotonia periodica. Thyroid and parathyroid therapy helps here. Parathyroid insufficiency induces trophic disturbances of the skin, nails and hair; myotonia, myoclonia, tetany, myoclonic convulsive movements and epileptic seizures. These cases do exceptionally well on an anterior pituitary combina-

tion with or without parathyroid. A large thymus is responsible for myasthenia gravis, undeveloped genitals and hypogonadism. This gland is small or absent in mentally-deficient and marasmic children.

Many children regarded as wayward, incorrigible, uncontrollable, irritable, precocious, masturbators, sexual perverts, and who have perverse tendencies, manifest congenital psychoses, psychophatic personalities and show signs of mild or severe forms of mental derangement, belong to the great group of endocrinopathies or pluriglandular dyscrinisms. We should group them according to their physical signs, whether they are of thyroid, pineal, pituitary, adrenal, thymic or gonad types, or a combination of these, and treat them accordingly. We must also include in the therapy the proper environment, proper diet, good habits, sex hygiene, and when necessary, drug adjuvants.

CONCLUSIONS

It appears that the ductless glands, which have common origin, are related in function, thus adrenalin and the posterior pituitary principle have a similar action; the anterior lobe of the pituitary body and thyroid extract are related in function and origin as also are the adrenal cortex and the gonads.

Metabolic control is governed almost entirely by the internal secretaions and, therefore, it plays such an important rôle in children's disorders during the growing period in infancy, childhood and especially at puberty. The carbohydrate metabolism is primarily regulated by the pancreas and adrenals, the former regulates glycogenic function and the latter glycogenic fixation. Protein metabolism is controlled by the thyroid gland and the destruction of purin bodies by the hypophysis, epiphysis and the thyroid. Calcium, phosphorous and mineral metabolism is influenced by the thymus and parathyroid. The thyroid, hypophysis and para-

thyroid glands also influence carbohydrate metabolism through a secondary influence on the adrenals and pancreas. The pituitary, thyroid, adrenals and gonads influence the metabolism of fat.

It is known that direct lesions occur in the endocrine organs and frequently certain clinical syndromes are connected with such lesions of one organ or another. Experience has shown that the endocrine organs are closely connected with each other functionally, so that a disturbance in one involves, according to the circumstances, a more or less profound disturbance in the function of a smaller or larger number of the others. From this we can infer that pluriglandular disorders are much more frequent than disorders involving a single gland of internal secretion and, therefore, the administration of one or more synergists or pluriglandular therapy, may radically alter the results in a given case for the better and determine the final outcome.

I regard endocrinology and organotherapy as of the utmost importance in both the diagnosis and the treatment of many of the problems of pediatrics.

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XIX

SOME THOUGHTS ON INTERNAL SECRETION

By Harry S. Noble, M.D., St. Mary's, Ohio

The Ancients evidently had a vague idea of internal secretion, and many records indicate that organotherapy was practiced by them. In case of disease of an organ, an extract of the corresponding healthy organ was given, taken from some of the lower animals. For instance, fox lung was given in phthisis, wolf's liver in jaundice, and ox eyes in ocular troubles. All knowledge of internal secretion, however, had its origin in the sexual glands.

Berthold, of Göttingen, in 1849, removed a cock's testicles, and found that the developmental changes in his voice, fighting spirit, comb or wattles were missing. This was not the case, however, when the testicles were transplanted to another part of the body. As a result of this it was then believed that every organ gave to the blood an internal secretion; and that if the system were deprived of this substance from one organ, another would rise to the occasion, and furnish a substitute.

Brown-Séquard really fathered the practical aspects of the theory of internal secretion, when in 1889, at the age of 72, he appeared before the French Biological Society, in Paris, and demonstrated on himself the effect of the testicular extract of the dog, when injected subcutaneously. It is said the effect was mar-

velous. His eyes brightened, his countenance became animated, his mentation was accelerated, and he took on a temporary vigor that was phenomenal, but as fleeting as a drink of whiskey. The sex glands immediately became the subject of the keenest investigation, and it was found that they have the greatest degree of autonomy. There is virtually no dependence whatever upon the central nervous system; for it was found that animals may conceive, and give birth to their young and suckle them, with their spinal cords severed. The ovaries may be removed from the pelvis, and tucked away in the axilla, without arresting menstruation, save for a month or two. The effect of the sexual glands on the body development and other glands of internal secretion is marvelous. For centuries it has been known that the castration of an animal increased its fat, and this operation has been employed by animal breeders for commercial purposes.

The influence of the sex glands is stimulating to the thyroid, and when this stimulus is removed, the lessened activity of the thyroid lowers oxidation and fat accumulates in the tissues. It is for this reason that many individuals take on flesh from 45 to 50. It is an indication of what has been termed "hypogonadism," —the testicles or ovaries are degenerating.

In the treatment of obesity, which can safely and surely be remedied by the administration of thyroid extract, the effectiveness of this medication is greatly enhanced by the addition of an extract of the corresponding sex gland. On the other hand, the pituitary (anterior) has a stimulating effect on the testicles; for when the greater part of this gland is removed, the testicles atrophy in a very short time.[1] Hence, in all conditions, where an increased action of the testicle is desired, combine pituitary with your spermin medication, and you will increase the effectiveness of your treatment.

To the sexual glands belong that rare and evanescent phase of life known as youth, characterized by an exuberance of spirit, and energy run riot, and physically, by the bloom on the cheek, the light in the eye, and that illumination of countenance, which has given rise to the saying that, "Even the devil was handsome when young."

Zoth and Pregl, by a series of carefully conducted experiments, have shown that greater vigor and an increased muscular capacity follows the oral administration of testicular extract.

The next organ to receive the attention of the physiologist, was the adrenal gland. It was noticed that during fetal life the adrenals were much larger than the kidneys; that at birth they are about equal in size, and that a process of involution is immediately inaugurated, which slowly brings about old age.

It was further learned that the organ is composed of two separate glands, which in the lower animals remain apart; that the upper or cortical portion had the greatest effect of all glands on general body development, the evolution of the organs, and the growth of hair. A tumor of this part of the gland will cause a child of 5 to appear 10, or even 15 years of age. In men of the Esau type, who have much hair over chest and abdomen, and women who have mustaches, there is an unusual activity of the cortical portion of their adrenals. Hemorrhage of the adrenals is far more frequent than is supposed, and is perhaps less frequently recognized than any other acute trouble in the body. Many a case of sudden pain in the abdomen, operated for appendicitis or perforation of the abdominal viscera, and nothing found, is a case of hemorrhage of the adrenals.

The one symptom of insufficiency of the medullary portion of the adrenals, is weakness and languor, with low blood pressure. Neurasthenia, accompanied by a

low blood pressure, as we so often find it, is most probably due to an insufficency of the adrenal medulla. And it is quite possible that the persistent weariness, and constant fatigue, which we have termed laziness, may have a similar origin. I have known many such cases to take on renewed vigor and energy following adrenal therapy. Adrenal medication should always include the whole gland, and I believe that it is more effective when combined with the sex gland, for there is an intimate relationship of function between the testicles and the adrenals.[2] The intermingling of the two types of tissues, and the similarity in action of the two active principles,[3] both of which resist boiling, is also well known. We may administer testicular extract to the female, because spermin is found in the blood in only slightly reduced quantities as compared with that present in the male.[4]

The antitoxic action of the adrenals has been positively established. A guinea pig may be given the 1/6 gr. strychnia, and if this is followed immediately by an injection of 30 minims of adrenalin, no harm will result. The same animal will die of convulsions if the experiment be repeated and the adrenalin omitted. This may account for the fact that chickens and quail are immune to strychnia, while crows are not. By the intravenous injection of adrenalin and artificial respiration, Crile has resuscitated animals 15 minutes after death; and he kept a dog "alive" for ten hours after its head was cut off, by means of adrenalin in salt solution.[5]

One can measure with reasonable accuracy the adrenal efficiency of a patient by his susceptibility to atropine and pilocarpin, for the individual who reacts strongly to these drugs is comparatively insensitive to adrenalin, and conversely. Individuals with large tonsils and much adenoid tissue in the pharynx, perhaps

associated with enlarged follicles at base of tongue, are very apt to have an insufficiency of the medullary portion of the adrenals. The person whose pulse is difficult to find, because of a small artery, or whose uterus is of the infantile type, many times is deficient, in this respect. While I never heard it said by others, I have nearly always found an adrenal medullary insufficiency in persons whose pupils are chronically large. Such individuals have slight resistance to infection, and they are bad risks for the surgeon as well as the anesthetist. On the other hand, one will occasionally find an individual in whom it is quite difficult to dilate the pupil, his pulse is large and full, his blood pressure up to the top of normal, and, perhaps, his temperature is slightly above normal. Such an individual has an especially active chromaffin system, and his resistance is good. He will perhaps not die of an infectious disease, but rather of diabetes, nephritis, pernicious anemia or liver disease. He takes an anesthetic splendidly, but may lose his life from the cocainization of a tooth for extraction. The possibilities of adrenal therapy are scarcely dreamed of as yet, even by the enthusiastic organotherapist.

Sajous says that carcinomatous and sarcomatous growths in rats and mice have been made to disappear under adrenin treatment.[6] Solis-Cohen reports some wonderful results in the treatment of cardiac as well as true asthma;[7] while Tyson and Jump claim to have cured abdominal ascites by the same medication.[8] Personally, I have seen marked improvement in bronchial asthma under combined pituitary and adrenal treatment; and in hay-fever I have known as much relief to follow an injection of Liquor Hypophysis as results from a quarter of a grain of morphia.

As for thyroid extract, remember that it contains nature's brand of iodine, as used in the metabolism of

all animals, and should be used wherever iodine is indicated. In long-standing cases of exophthalmic goitre, which have passed over into the myxedematus state, thyroid extract is the treatment *par excellence.* In keratitis, and iritis, with cloudy cornea and fluid, I have known it to work in a manner that was almost miraculous. The late Samuel D. Risley, famous opththalmologist, of Philadelphia, told me that in chronic inflammatory conditions of the eye, accompanied by opacities and indurations, he had frequently found thyroid medication of great value. Do not forget its use in fractures that are slow to unite, or of fecal fistulas that have failed to heal.

I have observed that sometimes when thyroid medication had failed, another package, put out by the same laboratory perhaps, would prove effective. It was very puzzling to me until I learned that Kendall, of the Mayo Research Laboratory, has found that the iodine content of the thyroid gland of the dog, the hog, the sheep, and the cow, was four or five hundred per cent greater in the summer months than in the colder season of the year.

In undersized children, or wherever else thymus or adrenal medication is indicated, in addition to such medication, instruct your patient to eat sweetbreads two or three times per week; for none of the endocrine glands play a part of selfish isolation, hence they act best when combined.

The sexual glands inhibit the thymus, as well as the pituitary. The pituitary in turn inhibits the thyroid and stimulates the gonads, while the thyroid inhibits the adrenals. This tangled skein of cause and effect, of influence and counterinfluence, of stimulation and inhibition, holds within its mesh the great future of medicine. And unto him to whom there is given an understanding of the laws of internal secretion, there shall be added all things else.

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XX

SOME NEW WAYS TO USE LIQUOR HYPOPHYSIS

By H. E. MacDonald, M.D., Los Angeles, Calif.

In the course of several years' experience with various perparations of the active principle found in the posterior lobe of the pituitary body, I have become accustomed to using this remarkable organotherapeutic preparation in several conditions for which I have not seen any recommendations in the literature. Also I have worked out a method of using Liquor Hypophysis in labor which differs materially from the procedures outlined in the works of reference at my command.

Gall Stone Colic

In biliary adrenal colic I give a hypodermic of morphine and after the pain stops I inject intramuscularly 1 mil. of Liq. Hypophysis. Ordinarily this brings the pain back, but within a few minutes the stone usually passes. In fact, I have never known it to fail in colic of either variety.

Acute Appendicitis

A few days ago I was called at noon to see a large man suffering extreme pain from an acute attack of typical appendicitis—it being the third time he was brought down by this disease. He refused to be operated. I relieved him of the pain with morphine and then injected 2 mils. of Liq. Hypophysis. He almost immediately had three "colicy" pains. Called at 10:00 P. M.; no return of pain. Next morning the patient

was up and said he had eaten his usual breakfast without discomfort.

A Routine in Labor

By the use of posterior pituitary extract, labor can be made a pleasure,—at any rate, my patients look back upon their confinement as a happy episode in their lives and they are unanimous in declaring they will not be afraid to repeat the experience. Here is what I would call "the super-relaxation method" of delivery:

As soon as labor surely has begun put the woman to bed without an examination. Place towels dampened in lysol solution over the vulva. Throw a sheet over the head of the bed. Saturate a towel with chloroform and pin it to the sheet about two feet above the patient's head. As this towel becomes dry, saturate another and pin over the first. (The drop method is intermittent compared to this.) In thirty minutes the patient is asleep. Shave the pubes and around rectum. Scrub with soap and water. Put on sterile leggings. Draw one-half a mil. of Liq. Hypophysis into a medicine dropper. Put a drop in each eye, two on the tongue and squirt remainder up the nose. Place two fingers of the gloved hand into the vagina and press gently, continuously and steadily backward. If this does not bring on uterine contractions inject ½ cc. Liq. Hypophysis under the skin above the knee. Continue the pressure alternating the hands as each may tire. This pressure and an occasional hypo. of Liq. Hypophysis will keep up uterine contractions while patient remains asleep. Eight, or even more injections may be given without harm, under such circumstances during the course of labor. In one hour the vagina should be large enough for the whole hand to be introduced into it, clinched and withdrawn without force. If the cervix is slow to dilate it may be stretched also. Insert two fingers of each hand and gently dilate. As the head appears, the

perineum is grasped with bare hand, covered with a towel rung out of lysol solution. The fourchette is thus kept relaxed as the head and shoulders escape.

The following advantages appear to be evident, as shown by 50 consecutive cases:

No pain from beginning to end of labor.

No danger to mother or child. (No mortality or morbidity.)

No forceps.

Almost no lacerations (3 in 50 cases). Birth of baby generally without a drop of blood.

No postpartum hemorrhage.

Short labor (average, 3 hours).

No postpartum fever.

No postpartum soreness.

No exhaustion. Patient is earlier at work.

No straining, hence no injury therefrom.

Easy asepsis at delivery.

Perfect control and examination of mother.

Easy examination of child in uterus.

No blue babies.

Second stage of labor not over 5 minutes in duration. No danger from cord around neck.

No shocking of the modesty of the mother.

Easy correction of faulty presentations.

Easy management of pathological conditions.

Easy delivery of placenta.

No assistants necessary.

All mothers can nurse babies.

All of which serves to encourage the bearing of children.

Another presumptive advantage which may be mentioned is that fewer, if any, cancers of uterus will occur in after life.

Disadvantages: If pituitary solution be given just before birth after pains may annoy. By holding the

uterus half an hour after expulsion of the placenta these will be prevented.

Precaution: Although pituitary extract is harmless in any ordinary amount in sleep, it should not be given by hypodermic to the pregnant when they are awake for fear of causing tetany. [Note: Many observers have remarked that the physiological action of Liquor Hypophysis (U. S. P.) is directly opposed to that of morphine and chloroform, and *vice versa*.—H. R. H.]

Addendum: In twenty cases I induced labor with happy results to baby and mother by insufflating powdered posterior pituitary substance up the nose, and then holding the tip of the finger against the external os for several minutes. In a few cases I found it necessary to hook the finger over the internal os.

XXI

THE FUNCTION OF THE OVARY AND ITS RELATION TO OTHER ENDOCRINE GLANDS

By James H. Hutton, M.D., Chicago, Ill.

In the July (1920) number of the *Yale Review*, Eugene Lyman Fisk gives as one of the conditions operating to shorten life, hormone deficiency. He says "hormone deficiency is probably the greatest immediate factor in limiting the life cycle. It implies a lack of some substance or group of substances whose function is to stabilize the tissues in a state of health." He enlarges upon the possibilities of a perfect hormone balance and, while some of his conclusions are avowedly whimsical, he emphasizes the importance of these "substances." While it is not certain that life could be greatly extended by regulating the "hormone balance," it is now conceded that perfect harmony among endocrine glands does make for normal development.

A marked discrepancy exists between the amount of definite work accomplished on the majority of the endocrine glands and that done on the ovary. The internal secretion of the ovary was among the earliest of the hormones whose existence was recognized.[1] It was also one of the earliest to be used therapeutically. In spite of this fact very little is definitely known concerning the nature of the ovarian hormone, or of the portion of the ovary from which it comes. Therapeutically, some claim the corpus luteum as the only useful active principle; others prefer the whole gland;

while at the present time one of the foremost gynecologists in the country is claiming good results from ovarian residue—that portion of the ovarian stroma which remains after the corpora lutea are all ablated. One thing can be said positively: preparations of ovarian residue retain their therapeutic activity longer and under more adverse conditions than preparations of or containing corpus luteum.

The fact that our exact knowledge of ovarian function is very limited does not prevent cases of disturbed function being widespread. And every practitioner meets them daily. Whether he recognizes them as such, or not, is an entirely different question. For this reason, I have attempted to present in a brief way the few facts that are definitely known concerning the ovary and its relations to the other endocrine glands, citing a personal case now and then for emphasis.

"The ovary governs all the important physiological activities of the sexual organs. It contains a portion whose secretion is external and upon which devolves the perpetuation of the race (ova) and an internal secretory apparatus (follicles, corpus luteum or interstitial gland), which exerts important influences upon the entire organism." [2]

The internal secretion of the ovary has never been isolated. Evidence that it exists rests upon the results of its extirpation and destruction experiments in animals and, to a less extent, upon clinical observations. These latter—so far as woman is concerned—have to do with observations following removal of the ovary, histological examinations after the menopause, and the results of transplanting ovaries or feeding various ovarian preparations. Quite naturally, there has resulted a number of divergent views and different theories as to the function of the ovary and its various components.

A few things the majority are agreed upon. In general, the total ovarian secretion tends to promote the excretion of calcium and the retention of phosphorus and it arouses activity in most, if not all, of the remaining ductless glands.[4] The implantation of the fertilized ovum is assisted by, if not absolutely dependent upon, the presence or internal secretion of the corpus luteum. The activity of the uterus is maintained and regular contractions are promoted probably by the secretion of the interstitial cells.[4]

The ovary produces at least two distinct internal secretions (some investigators believe there are more)[8] —one from the interstitial cells or stroma, and one from the corpora lutea. That produced by the former is indirectly concerned in the regulation of menstruation and nutrition generally. The corpus luteum sensitizes the uterine mucosa[2] and inhibits ovulation. It is also an important factor in the growth of the mammae. According to Osborne,[3] it is probable that one of the functions of the corpus luteum is to cause menstruation. Theoretically, its therapeutic administration ought to be valuable in the treatment of the nausea and vomiting of pregnancy, since the true corpus luteum is only formed in pregnancy, but in routine it has failed to have any definite value.[5] In this condition adrenalin has been of more service than any other endocrine preparation. I have had some very good results with it. Giving ten drops of the 1-1000 solution every four hours frequently has succeeded when other measures failed. Dr. Bloomfield informs me that he and the other members of the staff of the Chicago Lying-In Hospital, including De Lee, use it almost as a routine measure.

THE RELATIONS OF OTHER ENDOCRINES

The pineal gland is supposed to be antagonistic to the ovary, tumors that cause destruction of it tending

to precocious sexual development. This is not well proven. The thymus is also antagonistic; its abnormal persistence results in delayed puberty and sexual infantilism. If it atrophies early precocious puberty supervenes and the girl's growth is stunted, owing to the ensuing loss of calcium and consequent disturbance of bony development.

With the subsidence of the pineal and thymus there is left, in the adult, the thyroid, pituitary and adrenal cortex to reckon with in any consideration of the ovary. The action of the thyroid and pituitary upon the ovary is such that depending on variations in their functional activity "there is a normal menstruation, menorrhagia, relative amenorrhea, or varying degrees of actual amenorrhea." [5]

The menstrual history of a woman's life and the part played in it by the ovary and other endocrine glands is interesting. For approximately twelve or fifteen years the thymus dominates the situation and there is no development of secondary sexual characteristics and no menstrual flow. At the end of that time the ovary either begins to function or adds a new secretion to its repertoire and the thymus fades away. The thyroid certainly, and the pituitary probably, assume added activities at that time and the menstrual flow begins, a phenomenon that continues more or less regularly for about thirty years. At the menopause the ovary undergoes some atrophy and some related change of function, menstruation ceases and probably the pituitary becomes less active or ceases its endocrine service entirely. The rôle of the thyroid is disputed, some claiming that there is a hypofunction and others a hyperfunction. It seems to me about equally divided, some being influenced the one way and some the other. I hope soon to have something definite to say on this point by measuring the basal metabolic rate of a series of women at various stages in the meno-

pause. The adrenals take on increased activity at this time, enlarging after the menopause. It has been already proved there is more adrenalin in the blood after the menopause.

THE INFLUENCE OF THE THYROID

The thyroid hormone stimulates or supports the ovary. Menstruation cannot properly occur without it. If this stimulus is insufficient there is always a decrease or cessation of menstruation, according to the degree of insufficiency. Such cases are obese, lack energy, and are deficient sexually.

The more marked thyroid insufficiency which produces myxedema and is invariably associated with suppression of the menstrual function.[7] Marked hypothyroidism almost invariably results in sterility, while cases of minor or variable states of this disease improved notably when pregnancy occurred.

"Both the minor and the major states of thyroid insufficiency are readily amenable to thyroid treatment, with one reservation—if the girl has suffered from thyroid insufficiency for some years past the period of puberty, and has never menstruated, it may be impossible to relieve her genital condition, and the uterus may remain undeveloped. If the insufficiency has arisen after the subject has possessed full genital activity, then the uterus may, even after a long period of inactivity, resume its normal functions." [6]

With ovarian insufficiency hypothyroidism is much more frequent in young women, while hyperthyroidism seems to be more common in adults. Ovarian disturbances are almost always found accompanying hyperthyroidism. Osborne states that the ovaries are always over-stimulated when the thyroid is too active.[8] Early in these cases menorrhagia is common. Later amenorrhea is usual, but probably is due to a disturbance of the general metabolism. During the meno-

pause insomnia is frequent and may be extreme—the pathogenic factor is often a latent hyperthyroidism. On the other hand, a tendency to somnolence is due to thyroid insufficiency.

THE PITUITARY GLAND

The pituitary gland is so intimately concerned with the proper development and maintenance of the genital functions that an insufficiency of the pituitary secretion is likely to be associated with amenorrea or scanty menstruation. The *dystrophia-adiposo-genitalis* is supposed to be due to pituitary subsecretion—just as acromegaly is supposed to be due to an excess of secretion. But Bell points out that as amenorrhea is usually found in both conditions the explanation of the two diseases is not simple over- or under-secretion. Acromegaly is a condition producing masculinity and consequently amenorrhea. "While in *dystrophia-adiposo-genitalis* genital atrophy is invariable, yet, if functional activity has existed before the disease, activity may return on relief of the condition by decompression or by the administration of pituitary extract." [7] He suggests that delayed menstruation, accompanied by obesity, might be successfully treated with pituitary extract if the age of puberty were not too long past. In cases presenting obesity, mental dullness along with amenorrhea, thyroid extract followed by pituitary may be used. Better still, both may be given together. Deficiency of the pituitary secretion seems to cause under-development of the sex glands in youth and sexual inactivity in the adult.[8]

Bandler[5] believes that many of the functional dysmenorrheas are due to an excessive action of the posterior lobe. In my own experience, in one case of hyperovarism the periods were accompanied by terrific headaches. On several occasions these were markedly relieved by the use of pituitary whole gland.

THE ADRENAL MEDULLA AND CORTEX

The somewhat rare condition of osteomalacia is due, in part at least, to hyperfunction of the ovary, and castration affords the most prompt and permanent relief of any measure yet tried. Because several reports indicate that adrenalin has been successfully employed for the control of osteomalacia it may be reasoned that in this disease there is some adrenal insufficiency.[6] The adrenal medullary principle undoubtedly is antagonistic to ovarian secretion.

In cases of adrenal cortical hyperplasia amenorrhea is a constant phenomenon and in well-defined cases pregnancy never occurs. Amenorrhea is usually associated with Addison's disease (apparently the symptoms are chiefly due to insufficiency of the medullary secretion); but experimental evidence indicates that atrophy of the uterus, presumably with insufficiency of the function of the interstitial cells, occurs in these circumstances.[6]

Hyperplasia and tumor formation in the adrenal cortex are associated with extraordinary changes in the primary and secondary sex characteristics. In 1912, Ernest Glynn[9] exhaustively reviewed the whole subject, adding five cases in children to those already collected by Bulloch.[10] Out of seventeen cases in children, fourteen were females. In these the uniform findings were a marked skeletal overgrowth, increase in the amount of hair on the face and pubes, and sometimes an hypertrophy of the clitoris. Glynn also collected six cases occurring in young adult females, in all of whom there was growth of hair on the face, shrinkage of the breasts, amenorrhea, and sometimes a masculine voice.

This pathological evidence is of value since it shows how closely the adrenal cortex, which is developed from the mesothelium of the Wolffian ridge adjacent to the germinal area, is connected with the sex character-

istics. There evidently is some correlation between the two in normal circumstances.[7] In this connection, Falta and Meyer[11] state that "those adenomata of the adrenal cortex that are associated with hyperfunction of the cortex are of great interest in the study of the internal secretions. There is a difference in the clinical picture according to whether they develop in the entirely childish or in the juvenile or the adult organism. In the child there is an enormously accelerated development of the body, and premature development of the genitalia. The condition nearly always affects girls." So marked are the consequences that it seems evident that the secondary sex characteristics are dependent largely on the adrenal cortex.[11]

Hypo-ovarism is a far more frequent condition than over activity of the ovaries. The latter may occasionally be found in early life accompanying pituitary disease, abnormal thymus atrophy, or a pineal tumor. Resutling from the dyscrinism, the ovaries may function very early or abnormally and menorrhagia or metrorrhagia may develop. Consequently. the adrenal glands, being excessively stimulated by this abnormal activity of the ovarian hormone, may be depleted, resulting in the long periods of adynamia and asthenia so commonly seen in ovarian cases.[6] A too rapid loss of ovarian secretion causes depression and melancholic conditions.[3]

In menstruation, large amounts of calcium as well as other salts, are lost; consequently, too frequent or profuse menstruation results in too great a loss of calcium and other salts and the bones, hair, teeth and nails may suffer; and an aggravating nervousness, loss of sleep and irritability follow.[3]

Pepe[13] reports eleven cases of scanty milk secretion successfully treated by corpus luteum. He believes that there exists a hypogalactia concurrent with ovarian insufficiency, in which case the homo-organotherapy

by corpus luteum or ovary serves as a regular and efficacious galactagogue.

OVARIAN HYPERACTIVITY

Hypertrophy of the ovaries is perhaps always the cause of precocity in girls. Piccardo[12] is convinced that excessive function of the ovaries is directly concerned in the etiology of uterine fibromata. He suggests antagonistic organotherapy as treatment, the thyroid gland being his choice. Bandler believes hyperactivity of the pituitary may be an underlying cause of fibroids. Briggs, of Sacramento, believes fibroids are caused by hyperactivity of the ovaries and reports good results from mammary therapy.

As the mammary hormone is known to be antagonistic to ovarian function, the former is valuable in controlling over-function of the latter. Mammary extract is given in doses of seven to ten grains—or more—three times a day, for menorrhagia, metrorrhagia and uterine fibromata. It acts, according to Bandler,[5] particularly well when combined with anterior pituitary extract. I have had some favorable results with this method. Mrs. L., aged 35; periods always painful and profuse but of the regular twenty-eight-day type until about her 33rd year, when the interval was lessened to only seventeen days and the flow became more profuse. The uterus was larger than normal and hard. Mammary gland, ten grains t.i.d., lengthened the interval to twenty-three days and later to twenty-eight, and noticeably decreased the quantity of the flow.

I have tried mammary extract in several cases of menorrhagia, one case of fibrosis uteri and one apparently hyperovarism. The duration of the flow was shortened and the intervals lengthened.

PLURIGLANDULAR ASPECTS OF OVARIAN FUNCTION

According to Carey Culbertson "the climacteric is monoglandular only in its etiology: in its manifestations it is distinctly pluriglandular." [14] Marañon[8] in his monograph goes into great detail on this pluriglandular phase of the menopause. He believes that the ovarian secretion is not a single chemical entity, but a complex group of hormones each having a different activity. These he divides into genital, sexual and general hormones. The genital hormones control particularly the menstrual process, the sexual hormones conserve the morphological sex characteristics, and the general hormones influence and assist in all the functions of the organism. If the suppression of ovarian hormone function is gradual or physiologic, as in the menopause, the insufficiency of some of them is made up by others from remote sources. He feels that this explains the error of considering under one head all the disturbances which characterize the menopause. The failure of the menses indicates the disappearance only of the genital hormones which are probably elaborated in the corpora lutea. The other hormones, which apparently are produced in the follicular interstitial tissues, either may still persist, or disappear first, as the various clinical symptoms show. The menopause does not begin with the irregularity of the catamenia, but long before, with the appearance of the various general disturbances. The general symptoms of the failure of the ovarian hormones also persist long after the complete suppression of the menses. Therefore, the menopause must be considered only as a phase of the critical age, and not synonymous with it. The critical age is divided into three periods: the premenopause, the menopause, and the postmenopause.[8]

According to Marañon the adrenal glands do not follow the development of the other organs, but con-

tinue to increase in size and activity after the fortieth year. Hypertension is the expression of hypermedullary adrenal activity, in the adult; and this hypertension is an almost constant factor in the menopause "even when there is no arteriosclerosis or other pathologic cause for it." [8] This same writer states that nearly all the cases of hypertonic diabetes are seen during the menopause and are similar to those of adrenal origin.

Adrenal insufficiency is comparatively rare during the menopause, hyperadrenia being the usual condition; but on the other hand, such insufficiency is very common in young women and may become more severe on approaching the climacteric. There may be, at this time, melanoderma—a symptom of hypoadrenia.

The dying out of sexual activity is accompanied or preceded by a lessening of pituitary activity. So one may expect hypopituitarism to be associated with hyperthyroidism and hyperadrenia as the pathogenic basis for most cases of normal climacteric. It will be recalled that obesity and the weakening of the genital function are the two symptoms indicating subpituitarism.

ENDOCRINE ASPECTS OF THE MENOPAUSE

"The essential symptoms of the menopause are expressions of the endocrine disturbances making up the crisis. These disturbances are sometimes slight and sometimes severe, for the climacteric is influenced by the factors which act in all the endocrine states." [8] Chief among these factors are the previous sexual life, temperament and disposition, infection, intoxication and emotions. When the pituitary is markedly involved there is increase of fat, early cessation of the menses, the patient is apathetic and indolent. Almost without exception there is hypopituitarism. Hence, pituitary treatment is given for premature amenorrhea, with increase in weight.

The hemorrhages, usually considered as an indication of hyperovarism, are realy due to luteal insufficiency. Lack of this hormone commonly results in the excessive menstrual bleeding. When the ovarian factor predominates there are persistent and repeated hemorrhages with severe psychic disturbances. In such cases ovarian extracts, having coagulant properties, are beneficial.

Pharyngeal and oesophageal spasms are neurotic afflictions rather common during the climacteric, and ovarian insufficiency alone may be responsible for them.

Among the psychic symptoms of the menopause the most common are melancholia, paranoia and manic-depressive states. While "the pathogeny of these symptoms is as obscure as anything in psychiatry," [8] the hyperfunction of the thyroid and adrenals has an important rôle. "Hysteria is influenced unfavorably in the earlier stages of the menopause, due to the endocrine instability of this period. Later, when the ovarian function is definitely extinguished and the other glands which take part in the crisis have become stable, hysteria decreases or even disappears. Neurasthenia stands in the same relation to the climacteric as hysteria." [8]

Many unusual conditions are connected with dysfunction. According to Marañon: "Kraurosis vulva is directly dependent on ovarian insufficiency." [8]

Angioneurotic edema, the *adiposis dolorosa* of Dercum—all such conditions are believed to be "endocrine-sympathetic alterations." [8]

Twice as many cases of gout develop between the ages of forty to fifty as at any other time. Therefore, gout is related chronologically to the menopause. It corresponds almost always to thyroid instability. As for chronic rheumatism, ovarian insufficiency predisposes to it and the whole complex endocrine crisis of the menopause intensifies this predisposition.

In combating the numerous disorders which accompany the menopause, from first to last, ovarian medication is indicated and, of course, any other necessary medication compatible with it. There are three ovarian preparations available: total ovarian extract, extract of the corpus luteum, and ovarian residue. The second is indicated chiefly in cases presenting disturbances of the menstrual function only. As these are not usual at the menopause, extracts of the whole gland should be used, and the desiccated extracts are to be preferred. Each case, of course, should receive minute study to determine just what endocrine requirements exist.

The majority of cases suffer from hyperadrenia. But adrenal therapy may be given for the rare condition asthenia, pigmentation, and hypoadrenia. Mrs. W. illustrates the latter—40 years of age. She complained of epigastric pain an hour after eating, some nausea and great weakness; was badly constipated and had some hot flashes, though her periods were still fairly regular. She had had the "flu" five months previously and had lost some weight, but had never been well since the birth of her last baby five years ago. Family, past history and physical examination negative except for a low blood pressure. She had been in the County Hospital where her stomach contents had been examined three times. She was given ovarian substance, two grains; thyroid, one grain; adrenal, one grain; one capsule t.i.d. In a week she reported feeling much better, and in two weeks went out and got a job to help support her three children and drunken husband.

In any of these disorders it must be remembered that ovarian pain is rarely the fault of the ovary. In this connection Chipman[15] recalls the words of La Rochefoucauld, "Pain is the biggest liar in the world."

However brief this review of the subject, it suffices to point out the major interrelationship between the ovary and the other glands and the variety of their influences. Bell[8] puts great stress on the part the internal secretions play in forming woman's physical, mental and emotional states. He refers to Helmonts' statement, *"Propter solum uterum mulier est quod est,"* which Chevan later changed to *"Propter ovarium solum mulier est quod est."* Virchow in reiterating this added, "all the peculiarities of her body and mind —everything, in fact, which in the true woman we admire and revere as womanly, is dependent on the ovary." But in the light of the interdependence of the endocrine glands Bell suggests changing the statement to *"Propter secretiones internas totas mulier est quod est,"* thus modernizing the phrase.

On the whole then, with the ovarian and pluriglandular preparations, the physician has at his command powerful remedies. In the use of these the larger his knowledge of the interrelations of the whole endocrine system the more skillful will be his ministrations. James, the psychologist, said that in right thinking the first step is "to conceive the problem aright." This is equally true in diagnosis. Comprehension and appreciation of the significance, force and influence of these glands will enable the physician to place the blame more nearly where it belongs. The proper use of these derivatives may afford to the patient an escape from that physical and psychic state so aptly expressed by Charles Lamb as "the majestic isolation of pain."

Indeed, some knowledge of endocrinology is fast becoming an essential. To quote Garretson, "there is no branch of medicine which can be intelligently practiced without an understanding of endocrine function —therefore, the general practitioner, as well as the specialist, without a working knowledge of this subject and its practical application, is immeasurably

handicapped in not possessing one of the greatest diagnostic and therapeutic assets to be acquired in the successful practice of medicine."

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XXII

THE ESSENTIAL DUCTLESS GLANDS

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In the whole realm of medicine, there is hardly a more fascinating branch, one that is more interesting as to scientific facts, and more important as to its relation to physiological and pathological conditions, than endocrinology—that branch of medicine that treats with the so-called "ductless glands." Young in years, hardly half a century old, this branch of medicine boasts of a literature that, in its quantity and quality, surpasses the literature upon any other subject in medicine that has been taken up during a similar period. The enormity of the literature upon this subject can be grasped from the fact that, in the second edition of Biedl's "Innere Secretion," published in 1913, the bibliography alone occupies over 250 large octavo pages. Swale Vincent, in his book on "Internal Secretions and the Ductless Glands," cites over 2,000 titles upon the same subject; while Sajous, in his latest edition of "Internal Secretions and Principles of Medicine," brings forth almost 8,000 titles. "Endocrinology," a bimonthly periodical, reviews hundreds of titles in each of its issues. Such is the wealth of literature; such is the outpour of endocrinological thought in the recent decades!

And yet, when one considers the most wonderful facts brought out within our generation in connection with some of these miniature organs; when one is confronted with proof of their powerful influence upon all phases

of the life of the body—the growth, the sexuality, the emotions, the immunity—one wonders whether, after all, this avalanche of literature is keeping pace with the interest that the subject deserves.

In a short essay, limited in scope and space, one cannot go into the details of this subject. Those who look for details are referred to the substantial works of A. Biedl, "The Internal Secretory Organs; Their Physiology and Pathology;" Sajous' "Internal Secretions and Principles of Medicine;" Swale Vincent's "Internal Secretion and the Ductless Glands;" Falta's "Ductless Glandular Diseases;" Harrower's "Practical Hormone Therapy," and numerous other works. In this essay we will, therefore, merely outline rather roughly the salient points regarding some of the endocrine glands and their influence upon the organism and conclude with a brief mention of some of the potentialities that those glands hold out to us in the nearest future.

THE HORMONE PRODUCING ORGANS

As their name implies, the ductless glands are organs whose products, called hormones, have no outlet into the free surfaces of the organism, like ordinary glands do, but instead find their way directly into the blood stream, which, laden with such hormones, exerts its specific influence upon the living organism. Hence the term, "internal secretion." The branch of medicine that makes a study of the ductless glands and their internal secretions is called "endocrinology." The most known, because the most studied glands of this type, are the thyroid, parathyroids, adrenals, pituitary and gonads (testicles and ovaries). Others, perhaps less well known in their action, are the thymus, pancreas, spleen and pineal gland.

It seems that Nature, in her wise ways, fully appreciated the importance and value of these small organs in placing them in inaccessible corners of the organism,

like the pituitary gland; or connecting them apparently with other organs, as the adrenals and the parathyroids—thus protecting them from possible injury, and allowing them to produce their valuable hormones undisturbed.

Now, when the ductless glands are anatomically and functionally in a normal condition, the hormones that they produce are also in an equally normal physiological state, and are produced in just the right proportion to mix with the blood stream, and perform their proper functions. But, unfortunately, these glands, like the rest of the body, are subject to different attacks from outside or inside, with resulting dysfunction, be it the numerous pathogenic microbes that frequently infest the organism, or be it the various growths, benignant as well as malignant, that either compress or entirely destroy the affected gland. Under such pathological conditions the product of the affected gland will either be diminished or increased. This will manifest itself clinically in the affected individual by sharply defined symptoms, a syndrome, more or less complex, caused either by the hypofunction or hyperfunction of the affected gland, and the changes that this initial dyscrinism naturally brings about.

THE THYROID GLAND

As an illustration, let us take up a few of the well-known syndromes produced by a pathological condition of certain ductless glands. Compare, for instance, the symptom-complex produced by the extirpation of the thyroid gland as in cachexia thyroprivia with that as the result of increased activity of the gland, as in Graves's disease. The table below is taken originally from the splendid work of A. Kocher, of Berne, as cited by Biedl: (1)

CACHEXIA THYROPRIVIA

1. Absence of or atrophy of the thyroid gland, lessened circulation.
2. Slow, small regular low-tension pulse.
3. Absence of vascular congestion and coldness of the skin.
4. Indifferent expression, lacking in movement and vitality.
5. Narrowed, puffy eyelids.
6. Retarded digestive and excretory processes, small appetite, slight need for food.
7. Slow metabolism.
8. Thickened opaque skin, usually dry or scaly.
9. Short, thick fingers, frequently broadened at the tips.
10. Sleepiness and desire for sleep.
11. Retarded sensation, perception and action.
12. Mental vacancy and indifference, lack of emotion.
13. Awkwardness and slowness of movement.
14. Stiffness of the extremities. No tremor.
15. Retarded skeletal growth, short, thick, frequently deformed bones.

GRAVES' DISEASE

1. Swelling, generally diffuse, of the thyroid gland, hypervascularization.
2. Rapid, frequently tense, jerky, occasionally irregular, pulse.
3. Extreme excitability of the vascular nerves.
4. Anxious, roving glance which appears angry when fixed.
5. Wide open eyelids, exophthalmos.
6. Abundant excretion, generally abnormal appetite, increased need for food.
7. Increased metabolism.
8. Skin, thin, transparent, finely injected, moist.
9. Long, slender fingers, with pointed tips.
10. Insomnia and restlessness during sleep.
11. Intensified sensation, perception and action.
12. Mental whirl, excitement to the point of hallucination, mania, etc.
13. Perpetual restlessness and haste.
14. Tremor of the extremities, increased joint mobility.
15. Slightly built skeleton, occasionally soft and thin bones.

16. Constant chilliness.
17. Difficult and slow respiration.
18. Increase in weight.
19. Senile appearance, even in young people.

16. Unbearable sensation of heat.
17. Superficial respiration, slight expansion of thorax.
18. Loss of weight.
19. Youthful, luxuriant development, at least in the earlier stages.

One can see from this table how diametrically opposed to each other are the symptoms produced. In fact, we have before us two different types of individuals, whose physical and mental contrasts cannot, indeed, be more outspoken. While the symptoms enumerated in the left-hand table are produced by extirpation of the thyroid gland, we find more or less similar symptoms in cretins and myxedematous patients, whose thyroid gland is either atrophied or destroyed. On the other hand, when we consider the fact that artificial Graves's disease was induced experimentally by feeding individuals with the desiccated product of the gland, there can be hardly any doubt that this chain of different symptoms is produced in the first instance by the lack of the thyroid hormone; and in the second, by its overabundance.

It is clear that this thyroid hormone now isolated in chemical form by Kendall, exerts a powerful influence over the metabolism and nutrition of the organism, hence upon its growth and normal development. The normal senility and old age, like the premature senility of myxedema, might be the result of the same etiological factor, namely, the lessened activity of the thyroid gland.

In this connection we will cite again from Biedl (2) a very interesting passage: "The foundation for the theory that old age results from changes in the thyroid gland lies in the fact, commented upon by Horsley, that

in old age the thyroid becomes atrophied, its follicles shrink and retrogressive changes take place in the epithelial cells. This is reënforced by the fact that there is a profound analogy between the signs of advanced old age and those of myxedema. The falling of the hair and the dropping out of the teeth, the dry and wrinkled skin, the lowered temperature of the body, the diminished perspiration, the indolent digestion and consequent emaciation, the reduced metabolism and consequent primary deposit of fat, followed by emaciation, the atrophy of the sexual organs, the decrease of mental power, and the diminution of the activity of the entire nervous system—these are all symptoms that caracterize chronic myxedema."

Sajous (3) on the other hand, is inclined to think that old age has more to do with deficiency of the function of the adrenals. The truth, however, is that in old age all the ductless glands are undergoing atrophic changes, which may account for the symptoms of senility.

THE PARATHYROIDS

In close proximity to the thyroid gland lie four diminutive organs, called parathyroids, which were described first by Sandstrom in 1880. Though anatomically connected with the thyroid, their physiological functions are entirely of a different character. The removal of these small glands produces a typical syndrome. The patient acquires a tendency to spasms and convulsions,—which gradually assume the form of tetany, epilepsy, or even tetanus. The breathing becomes labored, and the body temperature lowered. Ptyalism and fetid breath are often present. The amount of urine is decreased and the urine becomes more toxic. Death usually follows in from three to five days.

The importance of these small glands seems to be in reverse proportion to their size. Their presence is

fundamental to life, because their hormones, apparently, keep in check the toxins in the blood, which, once liberated, cause havoc with the organism, producing syasms, tetany and other morbid symptoms that rapidly kill the patient. This view is expressed by Falta (4) from whom we quote: "The parathyroids would seem to furnish to the blood-path a hormone which renders innocuous poisons that exist in the body." This function he calls "the detoxicating function."

THE ADRENAL GLANDS

Now let us see what rôle the adrenals play in the organism. According to Sajous (5), "It is the adrenal secretion which, after absorbing oxygen from the pulmonary air and being taken up by the red corpuscles. supplies the whole organism, including the blood, with its oxygen. It is, as such, the oxidizing constituent of the hemoglobin, which, in turn, sustains tissue oxidation and metabolism." An excess of the adrenal secretion, as produced during infectious diseases, causes in the organism a heightened temperature, fever, due to the excessive oxidation that it causes. Thus the adrenal secretion becomes a powerful factor in the autoprotective apparatus of the organism. The vital importance of the adrenals is evidenced from the fact that the removal or destruction of these glands is followed by death of the animal.

In the so-called Addison's disease we have a symptom complex of adrenal insufficiency, or chronic progressive hypoadrenia. It manifests itself in hypothermia—the patient always feels chilly—in dyspnea, in progressive asthenia, weak heart action, and low blood pressure, in emaciation, anorexia, vomiting, diarrhea, in bronzing of the skin, in lumbar and abdominal pains, in a marked tendency to syncope, impairment of vision and hearing, in headache, irritability, hallucinations, delirium, convulsions, and finally in coma and sudden death.

A very different symptom complex is noted in conditions connected with hyperadrenia, where an excessive amount of adrenin is sent into the blood stream. This occurs when one or both of the adrenals are attacked by malignant tumors. Premature development is the most prominent symptom. Children appear to become rapidly grown-ups, not only in their size, but in their sexual development. So Sajous (6) relates of a case, reported by Owen Richards, where "a girl of 7 years was as tall as a person of 20." Add to it an obese body, enormous appetite and thirst, a swarthy or dark-hued skin, a harsh and deep voice, and you have the full syndrome of the condition known under hyperadrenia. [It should be remarked here that adrenin is the active principle of the adrenal medulla, while the rare condition of hypernephroma, just referred to, is essentially a hypertrophy of the adrenal cortex, which is an entirely different structure from the medulla, despite its proximity. —H. R. H.]

There is another rôle, however, that the adrenal glands play in the life of the organism, namely, the one which is related to the different emotions of the individual. In his excellent work, based upon numerous experiments, Cannon (7), the Harvard physiologist, established beyond doubt the fact that during emotional excitement, or painful stimulations, the adrenal secretion is increased. The significance of this increase becomes clear when we remember that the adrenals are antagonistic to the pancreas; that the increased adrenal secretion at the same time inhibits the action of the pancreas, sugar becomes liberated, which, as we know, is so essential in muscular exertion. At the same time, the increased adrenal secretion raises the blood pressure, which does not permit the waste products of the fatigued muscles to accumulate and clog its actions. Again, the tendency of adrenin to increase the coagulation of blood becomes an important factor at a time of

emotional excitement, when the individual is ready for any combat. In Cannon's own words, "It (adrenin) plays an essential rôle in calling forth stored carbohydrate from the liver, thus flooding the blood with sugar; it helps in distributing the blood to the heart, lungs, central nervous system and limbs, while taking it away from the inhibited organs of the abdomen, it quickly abolishes the effects of muscular fatigue; and it renders the blood more rapidly coagulable. These remarkable facts are, furthermore, associated with some of the most primitive experiences in the life of higher organisms, experiences common to all, both man and beast—the elemental experiences of pain and fear and rage that come suddenly in critical emergencies." A little further on in the same book Cannon (8) summarizes his conclusions in the following important statement: "Thus are the body's reserves, the stored adrenin and the accumulated sugar, called forth for instant service, thus is the blood shifted to nerves and muscles that may have to bear the brunt of struggle; thus is the heart set rapidly beating to speed the circulation, and thus also, are the activities of the digestive organs for the time abolished. Just as in war between nations, the arts and industries which have brought wealth and contentment must suffer serious neglect or be wholly set aside both by the attacker and the attacked, and all the supplies and energies developed in the period of peace must be devoted to the present conflict; so, likewise, the functions which, in quiet times, establish and support the bodily reserves are, in times of stress, instantly checked or completely stopped, and these reserves lavishly drawn upon to increase power in the attack and in the defense of flight."

THE PITUITARY BODY

If the common conception is correct that the best things come in small packages, the pituitary must be

one of the most valuable things in the human body. It is indeed very small in size, less than one gram in weight, and apparently somewhat heavier in females, especially during pregnancy. Like most precious jewels it is hidden away in the intracranial locker of the body, where, secure from outside attack, it sets rough-rider-like, in the saddle *(sella turcica)* and through the innumerable hormonic reins that connect it with the other endocrine glands, exerts a most powerful influence over the whole organism.

It is composed of two parts, the anterior and posterior lobes, whose active principles differ considerably from each other. As with all the other ductless glands, there are two conditions of dysfunction to be considered—the overactivity of the gland, or hyperpituitarism; and its lowered or lessened activity—hypopituitarism. Of course, due to the different physiological characteristics and relationships of the anterior and posterior lobes of the gland, there is some confusion yet as to the source of symptoms produced, though the work of Engelbach, of St. Louis, has clarified the matter.

As a type of hyperpituitarism, we will consider the disease known in childhood as gigantism, and in adults as acromegaly, or Marie's Disease, Marie (9) having been the first (in 1886) to give a full description of it.

Gigantism, or the excessive growth of the skeletal bones, results when hyperpituitarism occurs in a period before the epiphyses have joined, while acromegaly is the result of the same conditions occurring in the subsequent period of adolescent life, or to be more correct, gigantism may be regarded as the prodromic stage of acromegaly (10). It is possible, as Cushing (1) thinks, that the hyperfunctional symptoms in acromegaly are due to the hyperactivity of the anterior part of the pituitary, while the symptoms ascribed to hypopit-

uitarism are based mainly upon the hypofunction of the posterior part of the pituitary.

The main symptoms of acromegaly, outside of the excessive skeletal growth, are the enlargement of the nose, lips, ears, tongue, lower jaw, hands and feet. The skin appears to be coarse, rough, and thick, and often has a yellowish pigmentation. The patient acquires an enormous appetite—bulimia—and often suffers with very severe headaches (the organic "pituitary" or neighborhood pressure headaches).

In hypopituitarism, increasing obesity is the predominant symptom; dwarfism and infantilism, when the individual is attacked in childhood. Feminism—the tendency in males to acquire feminine characteristics as to the distribution of fat and hair, and also as to the change of the voice—is quite frequent; amenorrhea is the rule in women, and the sexual activities are lowered. Lowered temperature, low arterial tension and continuous drowsiness are also frequent.

The physiological hibernation of animals and the normal sleep of man may have an etiological connection in the temporary, suppressed activity of the pituitary. Adolescence and puberty are very likely controlled by hypophyseal hyperplasia. So may pregnancy, with its temporary enlargement of the lips and nose, with thickening of the tissues of the hands and feet, be regarded as an "actual transient acromegalic" condition (19).

THE GONADS OR ESSENTIAL SEX GLANDS

Now, just a few words about the influence of the testicles and ovaries and their respective hormones. The removal of the testes, or castration, produces a characteristic symptom-complex, seen in the eunuchs, the symptoms of which are described by Sajous (13) as follows: "A tendency to obesity of a feminine type, due to slowed catabolism of fats, scantiness of hair, deficient

development of the thorax, pelvis, and larynx, the voice remaining high-pitched, as in the child; the muscles lose their tone and the prostate and vesicula seminals fail to develop, the bones of the extremities, however, growing abnormally long."

Compare this symptom complex with the syndrome resulting from conditions where the testicles are in a stage of hyperfunction. We find here, as we found in hyperadrenia, an abnormal sexual and physical development; "a general growth in stature; a premature appearance of secondary sexual characters, such as growth of hair on the face in the male and in the armpits, and on the pubes in both sexes; development of breasts and generative organs; in short, all the signs of puberty." (14)

This similarity of symptoms produced by an increased activity of the testicles and the adrenals, led Sajous (15) to deny to the testicles a separate internal secretion. He believes in the existence of "adrenal rests" or small areas of chromaffin tissue outside of the adrenal bodies, as in the testicles, ovaries, and pituitary, the internal secretion of which would be identical with that of the adrenals.

The endocrine action of the ovaries in females is somewhat similar to that of the testicles in men, with slight modifications, however. The removal of the ovaries in the young leaves the sexual organs in an undeveloped state, while their removal in adults causes atrophy of those organs, the menopause and diminished sexuality.

Space and time do not permit us to analyze the internal secretions of any of the other organs, as the thymus, pineal, pancreas, spleen, etc. Besides, our knowledge of the nature of their hormones is still very scant.

ORGANOTHERAPY

There is, however, another important aspect of the study of the ductless glands that we may touch upon,

namely, the therapeutic one. If, as we say, the hormones have such a powerful influence upon the living organism as to affect its metabolism, influence its growth, transform its appearance, modify its sexuality, affect its psychical state, could not we, with the same hormones, artificially introduced into that organism, modify or correct certain pathological conditions, due to disease of one or more of the ductless glands?

In the attempt to answer this question the modern procedure, organotherapy, was born. I say "modern," because, after all, organotherapy in a crude, primitive form existed with the dawn of human life on this earth. Even in the time of Hippocrates the use of various animal organs was recommended in cases where certain similar organs were affected. Isopathy, a branch of homeopathy, after all, is nothing else but a crude form of organotherapy. The scientific organotherapy may be said to date from June 1, 1889, when Brown-Séquard, then an old man of 72, reported the results of the experiments he had carried out upon himself, by the subcutaneous injections of testicular extract. This gave the impulse for further experiments with extracts of different ductless glands upon animals and man. The isolation of the active principles of the adrenals and pituitary and the marvelous results obtained from their use in appropriate cases, stimulated further investigations on these lines. To Harrower (16), the practical side of organotherapy owes its inception, as he was practically the first who collected all the material upon this subject that had been lost in the numerous medical periodicals of all tongues, systematized it, brought order out of chaos, and presented it to the medical profession in a well-ordered, complete volume. [This is not quite true. The writer admits that he has had a hand in this work; but many others have been interested.—H. R. H.]

Just a few more words in conclusion: Endocrinology is yet in its infancy. The mysteries of the ductless glands and their hormones have just begun to be unraveled. Exact knowledge on their relations to each other, is still awaiting the tireless investigators, who will find in this work unlimited opportunities for great discoveries.

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XXIII

STERILITY, SEX STIMULATION AND THE ENDOCRINES

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In presenting this paper to the profession I feel that it is my duty to preface what follows by a few words in reference to the subject, in order that conditions regarding the contained facts be realized. Almost thirty years ago, Brown-Séquard published in the *Archives de Physiologie* a treatise dealing with his research on testicular organotherapy. He went so far as to offer himself as a medium, and had injected into his body a preparation prepared from the testes of a dog. He reported that almost instantaneously he was endowed with renewed vigor and virility: in his own words, "Considerable laboratory work produced hardly any fatigue, and to the astonishment of my two assistants I was able to work for several hours in a standing position."

Unfortunately, the charlatans of Paris commercialized this fact by promptly seizing Brown-Séquard's announcement; as a result the real significance of the facts established by this master was drowned by the acts of these unethical practitioners to mulct their susceptible patients of more money. Thus his work and its result fell into disrepute, and up to the present this bad repute has stayed with organotherapy, whether it be testicular, or what not. Nevertheless, to those of us who have become interested in endocrinology, the facts presented in rough form in 1888 have formed a basis on which to work miracles in spite of the ever unfor-

tunate and cold reception given the perpetrator of any new method of procedure of robbing life of its degenerations or bringing back the sex instinct with its consequent happiness of mind and healthiness of body.

Volumes have been written on the subject, and there have been many criticisms offered. Testicular and ovarian organotherapy have suffered most. In my estimation three-fourths of the unkind things said about this branch of endocrinology have been the result of expecting the miraculous to happen, and the setting of one's hopes too high. Again many failures have been due to slipshod methods and treatment. Results have not been obtained in short intervals, and as a consequence the treatment has been abandoned.

AN INDIVIDUAL IS AS OLD AS HIS INTERNAL SECRETIONS

Senility and presenility, in my estimation, are nothing more or less than a waning of the endocrine function, accompanied by functional cellular inactivity, with the resultant increase in toxemia, which poisons and degenerates; repair, if it does take place, is slow, and the organs gradually fall into disuse, followed by atrophy. Ideals, ambitions and desires are but memories, while procreation is impossible.

When the ability to procreate wanes, the individual is then to be considered senile, unless the causative factor is a specific disease. This hypogonadism may exist at any period. It is seen during early adult life and is then due to indiscretion, or is the result of presenile changes in the internal glandular system, as portrayed by malnutrition, wrinkling and shrinking of the skin. The eyes become dull and the movements slow, while the spermatogenic function, as well as the ovarian sequence, disappears. This presenile stage may be also initiated by indiscretion, as shown by the sex glands becoming functionally inactive, and the case

may present the same hypogonadism that is found in pathological conditions.

I quote the following from an author who is evidently of the same opinion as myself:

"The diagnosis need not be discussed further, and its successful control through a mythical *elixir vitae* has been the goal of many from time immemorial, and from Ponce de Leon to the present day. Hypogonadism may be amenable to organotherapy even in elderly men, and the fundamental principles of homostimulation holds good in proportion to the responsiveness of the glands thus stimulated. It is a broader matter than the gonads alone, as the thyroid, pituitary and other endocrine glands all play their part. Senility then is hypocrinism rather than hypogonadism alone, and if we must treat it, it should be treated in the larger sense, and when organotherapy is in mind, it should be pluriglandular therapy.

Thus the failures of the past have acted as stepping stones to a more thorough investigation and firmer understanding of the subject. The solution of the vital functioning of the body depends on endocrine secretion, as do the senile and presenile phenomena.

SENILITY AN ENDOCRINE MALNUTRITION

Senility or old age is inevitable. It is the logical termination of the human organism. The allotted time of three-score years and ten, however, is only traditional, and there is no scientific reason why the human being must wither and cease to become a functioning factor after this time. We have accepted the age of seventy as the time for dysfunction, because we have had no specific therapy to combat its ravages. In other words, we have accepted the ultimatum because we have had no argument in the form of resistance to combat its ravages.

Senility is not dependent on the age of tissue, but on the condition or nutrition of that tissue by internal glandular functioning. Lack of functioning is inevitably followed by atrophy, while atrophy is followed by death. Dysfunctioning of the endocrine system regardless of age is followed by senile or presenile changes. In the young we find these conditions simulating changes that take place in late life, all due to singular or pluriglandular dysfunction of the internal glandular system.

The internal glandular system throughout life is capable of rendering its specific stimuli against a certain amount of resistance. If called upon, or taxed at any period of time, beyond its maximum output, fatigue results, with a retardation of function. Following this senile changes occur: a concrete example being in the roué whose spermatogenic function is at a minimum, also as shown in the neurotic individual who suddenly flares into tempers, only to call forth the adrenal secretion which in the end fatigues the gland, and due to a decrease in pressure caused by said fatigue the patient becomes asthenic. Again the unconscious dysfunction, such as decrease in the secretion from the anterior or posterior lobes of the pituitary, the thyroid persistance of the thymus, all have their effect on tissue nutrition. Activity of mind and body are registered on the dial of life in proportion to the nourishment of said tissue (not the age of tissue) which is dependent in great part by activation by the endocrines.

ENDOCRINE ASPECTS OF DEATH

Death in the broad meaning of the word as applied to the animal organism is always specific; it is due to lack of internal secretions to prevent their atrophy and death. Death is always due to cessation of vital function, caused in each and every case by the absence of that factor which under normal conditions activates or

keeps active vital function, the endocrines. Disease, aside from severe traumatisms, causes in the organism a toxic condition which retards by action of the degenerative changes produced the delicate metabolic equilibrium, and as a result death ensues either from paralysis of the respiratory center or a failure of the myocardium. In other words, the endocrines are reduced to a minimum, activation ceases and death ensues.

In nineteen hundred and fourteen it was my privilege to be in Bahia, Brazil, at the time Dr. Fernandez, a Spaniard, was using with some success a pluriglandular serum in treating sex conditions, such as sterility in the young female. His method was to give an injection of his product intramuscularly twelve hours previous to the act of intercourse. He was able in a series of twenty cases to induce pregnancy in two women so treated. All applicants were examined previous to injection, and any visible gynecological condition, such as atresia, or malpositions of the uterus were eliminated.

Dr. Fernandez's work on the internal secretions interested me, and as I was personally interested in metabolism, I devoted my time to its study: not, however, from the viewpoint of sterility, but metabolism in general, especially diabetes mellitus. In March, 1919, I published a paper dealing with the treatment of diabetes by the Edgar serum. At a later date a second paper was presented dealing with cases treated. At this time I was impressed with the number of patients who showed improvement in their sex relationship. Other patients manifested improvement in their mental condition. I became interested and found that many patients regained the power of erection and ejaculation. I became interested in the surprising results and immediately studied a series of cases that were not diabetic, in order to check up my results.

CLINICAL EXPERIENCES WITH PLURIGLANDULAR THERAPY

My idea in presenting this short paper is simply to place myself on record as being interested in sex stimulation and at present using a pluriglandular endocrine serum with success in the treatment of this condition. It was not my intention originally to depart from the specific therapy of diabetes, but my unusual observations in the cases treated have been so promising in producing a state of well-being in my elderly adult patients, that I feel entitled to state that I have a distinctly beneficial serum for the alleviation of presenile and senile deficiency: and that my product is capable of producing a new lease of life in those whose functions have been reduced to a minimum.

Previous to reviewing several cases, I may state that as I did not decrease the diets of these individuals, or try to build up their tolerance by starvation, I do not feel that their improvement was due to this form of therapy. Secondly, the last three patients were not diabetic, and presented no evidence of any objective or subjective disease, aside from their presenile conditions.

CASE I.—Male, aged eighty-four. Consulted me because he was losing weight and becoming weak. Complained of frequent urination, loss of memory. The patient had been employed by one of the large periodicals as a political writer on account of his intimate knowledge of politics. For the past six months he was unable to deliver any speeches, and because of his inability to concentrate was unable to write. Physical examination revealed a remarkably well preserved individual, skin ruddy and moist. The radial and temporal arteries only slightly sclerotic; eyes clear and moist; knee jerks absent; venereal history negative; fine tremor of hands present; musculature flabby; weight 210 pounds. The patient consulted me on account of his mental condition, thinking it might be due to diabetes, which was sapping his strength, and causing him

loss of sleep. I informed my patient that I did not think it wise to treat the diabetes heroically, as we might upset his metabolic equilibrium, as is often done in elderly diabetic patients when the diet is radically changed. He persisted, however, in his desire for treatment, and it was administered with reluctance. The injections took place as follows: September 10th, September 25th, October 4th, October 18th, October 27th, November 7th. At this time my patient voiced the opinion that he was feeling ever so much better, and that his memory had greatly improved, so much so that he had written an article for a Washington paper which had been accepted. He then received injections on: November 18th, November 28th, and December 15th. The patient was so much improved mentally that he was busy writing every day; his mentality was that of a man of forty. He was able to express himself in definite terms, and recall past events that had happened in the political world years ago; sleep was undisturbed. He informed me that he did not become fatigued on exertion, either physically or mentally.

During the course of treatment his sugar output remained unchanged, although the polyuria and weakness disappeared. This is a remarkable case in that definite results were produced in a man of this age, as evidenced by a dismissal of all symptoms that might be referable to a final waning of all endocrine functioning.

CASE II.—Young man, aged thirty-four, instrument maker by trade; venereal history negative. A history of diabetes extending back three years. Complained on visiting me of general weakness, loss of weight and ability to concentrate. Sexual instinct at a minimum; erection impossible. Physical examination revealed a prematurely old man. Skin dry with beginning wrinkles; heart and lungs negative.

First injection October 17, 1919, continued for a period of four months at intervals of seven days. There was no dietetic treatment advised, and none indulged in. On discharge, the patient was sugar free, had gained thirty pounds and, as he expressed it, was feeling like a new man. He also gained back the power of erection. His spermatogenic function, which had been absent for two years, returned gradually. His wife became pregnant in May, 1920, seven months after the

patient received his first injection, but unfortunately miscarried at the third month. He now enjoys better health than at any time during the past five years, and is doing hard manual work without any appreciable fatigue.

CASE III.—Female, married; no children. Menstruated at the age of fifteen. Periods remained regular until the age of twenty-seven, usually lasting four or five days; no pain. At this time the patient came home one evening to find her cousin dead in bed. Following this shock she swooned, was revived and continued in her usual good health, but did not menstruate. She had suffered from amenorrhea for the past two years, previous to consulting me. Physical examination revealed no obstruction or malposition of the uterus. There was no tenderness over the ovarian area, nor was there any leucorrhea. Skin was slightly icteric, and drawn in appearance. Frontal headache was complained of. The patient presented an apathetic appearance.

A specimen of the husband's semen examined on a warm stage microscope showed very active spermatozoa. His Wassermann was negative, as was that of his wife. I advised routine injection of my serum. The patient received one injection weekly for a period of four months. During the middle of the fourth month she menstruated. I visited her the following day, and found that she was losing a normal amount of menstrual blood. The flow continued for two days and subsided. The next period was regular, and they have continued so to the present. This patient had been curetted previous to the administration of the serum, without result. Undoubtedly her ovarian dysfunction was due to the sudden shock she received over two years ago, and as a result her endocrine equilibrium was disturbed and normal stimulus did not take place.

CASE IV.—Male, aged fifty-seven; hatter by trade. History elicited the fact that the patient's skin was becoming dry and rough. The sexual function had been impaired for the past four months, with inability either to ejaculate or maintain erection. The patient was unable, at times, to sleep more than two hours a night. He became uninterested in his work, lost weight and strength, and presented an apathetic appearance. The

physical findings were negative througnout, except for a slight hypertrophy of the prostate. There was a definite mental obsession due to anxiety over his condition. After receiving ten injections of the serum the patient had improved greatly and had resumed business. His nights were comfortable, and he felt much improved. Three months after beginning treatment he gained back the power of erection and ejaculation. Microscopical examination of the semen, however, revealed the fact that the spermatozoa were not motile. The psychological stimulus coincident to the return of the function was indeed wonderful in that it changed the mental aspect entirely, allowing him to dispel the pseudo-obsession under which he was laboring. This patient is well and working eight hours every day. His mental attitude is cheery, and he looks and acts twenty years younger.

CASE V.—Capitalist, aged fifty-four, past history negative as to medical and surgical illness. Has always indulged in alcohol to excess. History of sexual indiscretion dates back for the past twenty years. Consulted me June, 1919, because of inability to maintain erection, with partial loss of ejaculative powers. This condition had been present for a year. Physical findings negative aside from hypertrophied prostate. Administration of serum commenced June 15, 1919. Received ten injections in all. On discharge function had returned. I may state that there was no medication aside from the serum used in this case. This patient was of the roué type and the condition was the result of fatigue of the endocrine secretion which responded to specific stimulation in the form of activating substances.

CONCLUSION

In none of these cases was there any evidence of disease of the interstitial cells of Leydig. In each case electric stimulation caused a slight erection of the penile musculature, with a short contraction of the sphincter muscle. The patient in Case II did not react in any way to large doses of strychnine, which led me to believe that neurological conditions existed. In

spite of this fact endocrine stimulation produced results. Last but not least, the psychological effect produced by the renewing or revitalizing of a dormant function was capable in these five cases of so changing the outlook on life that bodily vigor and mental activity were substituted for morbid forebodings.

The question of grafting or implanting testes is a satisfactory procedure in the majority of cases, but as sex dysfunction is pluriglandular in its entirety, it is necessary to ascertain the metabolic rate and function quotient of the other secretory glands before operative procedure is advised. In a testicular implant case in which operation was performed some time ago, it was necessary to resort to thyroid feeding after the implantation in order to co-ordinate the *vis a tergo* of the secretory equilibrium, the patient being myxedematous as well as suffering from hypogonadism.

I am now working with a solution composed of the salts of the blood, the concentration being isotonic with the blood serum, into which the gland of the donor is placed to facilitate its state of resistance, during the interim between removal and implantation. By this method the functioning power of the gland may be kept in a highly nourished state. The spermatogenic function of the testes is not endogenous, but pluriglandular in its sequence. In other words, sex dysfunction, or testicular dysfunction, is hypoendocrinism, rather than hypogonadism.

XXIV

A SUCCESSFUL TREATMENT OF PERNICIOUS ANEMIA

By Chas. A. Ellis, M.D., Denver, Colo.

Pernicious anemia is characterized by a low percentage of hemoglobin in each red blood corpuscle, an unusually small number of red blood cells per cubic millimeter of blood, while the proportion of white cells varies from below normal to several thousand above normal. The sizes and shapes of all the cells, and especially the red cells, are more or less markedly irregular. The color index is one plus or more. The hydrochloric acid in the stomach is less than normal or entirely absent. All cases usually show a temperature variation of from one to three degrees from the normal. There is usually a peculiar lemon color of the skin. Marked asthenia and malnutrition necessarily is the rule. Relapses or exacerbations of this condition are very frequent.

The Chief Cause of Pernicious Anemia

The essential underlying cause of pernicious anemia undoubtedly is chronic septic absorption from various sources, viz., syphilis, tuberculosis or chronic appendicitis; a septic gall bladder; abscess of the prostate, fallopian tubes or pelvis; gonorrhea; infected tonsils, pyorrhea and subdental infections; malaria; rheumatism, etc.

The diagnosis is quite easily made by the blood count, the hemoglobin test, the color index, the estimation of free hydrochloric acid in the stomach. The blood find-

ings, and especially the abnormal appearance of the erythrocytes are considered to be pathognomic.

ENDOCRINE ASPECTS OF PERNICIOUS ANEMIA

The hemopoietic organs have been frequently connected with the glands of internal secretion and by some are believed to have an endocrine function all of their own. Be that as it may, the hormones, or active principles of the glands, evidently exert a sufficiently well-marked control of blood production as to render this aspect of the study of pernicious anemia of extreme importance. As will be seen hereafter in our consideration of the treatment of this disease, especial efforts must be directed at the removal of the cause, and this is preeminently proper; but the associate reëstablishment of a more nearly normal function of those hormone-producing glands which are responsible for the maintenance of those factors which regulate hemopoiesis, must be cared for simultaneously, and this is the explanation of the advantages which I have secured from the adjuvant use of organotherapy in the routine treatment of pernicious anemia. The thyroid gland, called by one writer "the keystone of the endocrine arch," certainly plays a very important part in the symptom-complex of pernicious anemia and efforts to reëstablish normal thyroid function add materially to the advantages of other indicated treatment. The adrenal glands evidently also have something to do with this condition, and since adrenal insufficiency is a very common occurrence in pernicious anemia the principles of adrenal support which constitute an important phase of organotherapy apply with equal force in these depleted, asthenic individuals.

THE METHOD OF TREATMENT

The positive locating of the causative infection is essential, and it is important, as the character of the

infection will indicate the serum or phylacogen to be used in the treatment. Naturally, this cause must be removed if any permanency of results is expected from the treatment.

If the hemoglobin figure is below 40 per cent., transfusion from a properly grouped donor should be performed at once and should be repeated once or twice as the results from other treatment are far from satisfactory.

The treatment is begun with suitable injections of a vaccine or filtrate similar to the phylacogens to correspond with the character of the infection present. If syphilis is the underlying infection, transfuse first and begin at once with a vigorous antisyphilitic treatment. Many cases not of syphilitic origin may give a weak positive Wassermann reaction, and in these cases continuation of the antisyphilitic treatment does no permanent good. The absence of a suspicious history, scars and other marks of lues should help to make the diagnosis, and with a negative Wassermann the reverse holds true. Any suspicion of an old syphilis should be sufficient reason to begin at once with the routine potassium iodide solution together with intravenous and other indicated medication.

Next in importance in the treatment of these cases is the use of the sera, since it has been found that their use in cases with a negative Wassermann frequently may change it to positive. As long as they cause a reaction in reasonable doses it is absolutely imperative to continue their use. If the Wassermann test becomes positive, active and prolonged antisyphilitic treatment is called for. It is of great importance during this time to use generous doses of products that stimulate the ductless glands. This is a phase of the treatment that must not be overlooked as many cases refuse to make a gain until after ductless glandular therapy has been vigorously and persistently used. Arsenic and iron,

alternating every other day, may aid in reëstablishing the activity of the blood-making processes. In nearly every case, in my experience, some form of the iodides, usually as syrup of hydriodic acid, has been of great adjunct value.

Since many cases of pernicious anemia are in need of digestive assistance, the administration of diluted hydrochloric acid and essence of pepsin in large doses should be persistently continued until the stomach is capable of resuming its normal function. Hemoglobin, with suitable endocrine reënforcement, is a very successful aid, and it should be pushed to the physiological limit. It is well to cease entirely with the organotherapy for five or ten days, and then push again as before. During all of this time if the patient is kept in bed, in the fresh air and sunshine when possible, the results are very much more satisfactory, as even a small amount of muscular exercise seems to destroy the results that are so hard to obtain. It has been found that frequent relapses occur after exercise, that do not occur with a prolonged rest in bed until the cells are well above three million and the hemoglobin above 65 per cent.

Tonics, aids to digestion, and, in fact, all supportive measures as, for example, diet for the building up of tissue and hygiene for the prevention of toxemia, will be of great assistance and will give the patient the uplift that is so much needed.

That the benefit obtained from this line of treatment will last indefinitely is, of course, problematical. Clinical cases remaining well for from three to six years, and who are still going on with their usual occupations with no relapses in that time, offer a degree of encouragement that no other treatment affords. Provided the source of infection is satisfactorily removed and the system is thoroughly stimulated and immunized by the serum and built up by the means before indicated, re-

lapses should not occur without a reinfection, and if they do, the reason is a matter which only time can elucidate.

CLINICAL REPORTS

The cases which follow are briefly reported to indicate the character of the success of this treatment:

Mrs. M., 34 years old; was a typical case, and had had three serious relapses. Several bad teeth and both her tonsils were first removed. The active treatment was begun by giving one mil. of Mixed Infection Phylacogen, which dose shortly was increased to 5 mils. daily. The injections were continued for two months. To this was added a simultaneous course of tonics, and the patient was kept thoroughly at rest in bed. The nutrition and blood count were remarkably increased, and she has remained normal for five years.

Mrs. J. had suffered from repeated attacks of quinsy. The blood picture was typical of pernicious anemia. Relapses were severe and frequent. She had been ill for two years. Both tonsils were removed. Treatment was as outlined above, which resulted in complete and full recovery, which has lasted for over five years.

Mr. D., 34 years old, ill with typical pernicious anemia for four years, and during that time he was under the care of at least six prominent Colorado physicians. Hemoglobin was below 30. The only history of infection that was discovered was an attack of jaundice ten years previously. An anal fistula had been operated on and cured two years before (two months before the operation a rectal abcess had developed and the fistula thus only had lasted two months). When he came under my care he had been suffering from repeated slight attacks of jaundice. The feet and legs were swollen to the knees, and there was an extreme weakness. The treatment consisted of one mil. Mixed Infection Phylacogen gradually increasing to five mils. daily, alternating with injections of three-grain doses of a solution of sodium cacodylate. Heart tonics were necessary for a time, and essence of pepsin was also given for the digestion. Thyroid was given in small doses. The patient came to the office with great difficulty and remained at rest in the intervals at home. The prognosis of several

physicians was that he would not live one month. Five months after treatment was initiated, he passed the army examination and worked in a chemical laboratory during the balance of the war. Since his cure he has remained well and very active. The blood count and hemoglobin are normal, and the color index is below one. He has been in perfect health for over two and a half years.

Mr. C., aged 34 years, was transfused at Rochester, Minnesota, sixteen times. He also had twelve intravenous injections of Neo-Salvarsan, as he had shown a slightly positive Wassermann, despite the fact that there was no known infection. The condition from which he suffered was diagnosed as typical pernicious anemia and not syphilis. The cause was diagnosed by me as due to an infected gall bladder, and after three months of the above treatment, the blood was tested and the hemaglobin found to be 80 per cent., while the red cells were 3,800,000 with a white count of 6,000 per cu. mm. The food was digesting well and at this time the gall bladder was removed, forty-two stones having been found therein. Unfortunately, the renal function seemed to have been paralyzed from the anaesthetic and there was complete anuria after the operation. The patient died forty hours later from uremic poisoning.

Mr. C., aged 56, ill for four years. Pernicious anemia was first diagnosed in Chicago, and later in St. Louis. He went to Rochester, Minn., where the diagnosis was confirmed and had over twenty transfusions of blood at various places.

The blood findings were as follows: Hemoglobin, 20 per cent.; red cells, 1,000,000; white cells, 3,000. A history of an old peritonitis was the only evidence of a previous infection. The urine was found to be loaded with bile and treatment similar to that mentioned above was carried out. The appetite did not seem to be particularly bad, and during treatment it became still better. The blood findings increased to hemoglobin, 44 per cent.; reds, 2,000,000; whites, 5,800. He then suffered from an acute dysentery, which lasted forty-eight hours, and died. The post mortem disclosed a greatly distended gall bladder, an old septic appendix, and adrenal glands which were almost entirely obliterated. No other striking condition was found.

Mr. E., aged 51, ill for four years. Hemoglobin, 47 per cent.; reds, 2,200,000; whites, 3,800. The prostration and weakness in this case were unusually great. He was nine months under treatment during which time he had a number of bad teeth removed. He also evidently had an infected gall bladder and pyorrhea. He had previously received ten transfusions and following the routine treatment already mentioned, is now apparently in perfect health, with a normal blood picture, at his usual occupation, with a weight increase of twenty pounds.

Mr. G., aged 64 years. Condition diagnosed as pernicious anemia at Rochester, Minn. Had had three transfusions with no permanent improvement. He had a condition of pyorrhea, which involved all the teeth. The history indicated a gonococcus infection four years before, with no other infection. All the teeth were removed. After a few injections of Gonococcus Phylacogen, a prostatic abcess was developed which, on draining by incision, evacuated over six ounces of pus. Gonococcus Phylacogen was continued with hydriodic acid and other tonics, including thyroid by mouth. Rapid improvement, full recovery and the patient has now been well for three years with no relapses.

Mr. N., aged 41 years. History indicated that he had suffered from a rectal abscess two years before. The hemoglobin index was 32 per cent. The blood picture of pernicious anemia was typical. In general, the treatment was given as above and recovery to a normal blood picture was accomplished in four months, since which time he has continued well and at active work.

Mrs. P., aged 40. Had a very serious attack of influenza in 1918, since then has been repeatedly jaundiced. The history shows that she has suffered from anemia for four years, and at present the hemoglobin is 40 per cent., the red cells 1,104,000, and the microscopical examination of the cells indicates their markedly deranged shape and size. The above treatment has caused rapid improvement and she is still under my care.

Mr. P., aged 45. This man has suffered from jaundice, which has extended at times as long as a year. He has had an infected right antrum, following an injury to the face. All the teeth had been removed. Transfu-

sion at Rochester, Minn., several times, with no benefit seeming to follow. Hemoglobin was 26 per cent., red cells 1,150,000, and white cells 2,000. He arrived in Denver unconscious, and shortly after had a severe attack of dysentery. He was transfused twice, and the treatment, in a general way, as outlined, was begun. There was marked improvement in one month. At that time the hemoglobin was 55 per cent., the red cells 2,270,000, and the white cells 6,000. He is now eating heartily and digesting his food satisfactorily and is still under treatment.

Mrs. H., aged 39. Had typhoid fever at twelve years, appendicitis at fifteen, and was never strong thereafter. In 1918 she suffered from influenza and since that time a condition diagnosed as pernicious anemia has been steadily developed. At present the hemoglobin is 24 per cent., the red cells 2,700,000, and the white cells 3,000. The improvement since treatment has been steady, and she is now able to do much of her own housework with no relapses to date.

Mr. A., 31 years old. Suffered from a constant cough with free expectoration. Wassermann test negative. Had suffered from jaundice four different times, and at present the urine contained bile. The amount of urinary solids was three times the normal and of uric acid, five times the normal. There was a large mass over the stomach, vomiting and diarrhea. The hemoglobin was 25 per cent., red cells only 1,000,000, and the white cells 6,800. Microscopic examination showed marked irregularity as to size and shape of the red cells. The legs were swollen to above the knees and the man was able to walk only a few steps, and suffered from extreme dyspnea. Before the laboratory test was finished he became delirious. Seven hundred and fifty mils. of blood were transfused from group four. He regained his mind and activity somewhat. After the use of Mixed Infection Phylacogen he again became delirious and the temperature rose to 103, pulse 140. He was transfused again the fifth day for the second time, at this time he was in a muttering delirium and fought the transfusion. Began the administration of 30 grs. of potassium iodide and soon increased the amount to 60 grs., four times a day, continuing the Mixed Infection Phylacogen and increasing the dose to

five mils., until no reaction was found. He became conscious on the third day, took nourishment the fourth day, and following this time daily injections of mercury salicylate, one and a half grains, were given. In two months' time the tumor disappeared, the liver dullness was nearly normal, and the patient was walking around and coming to the office for treatment. The potassium iodide was continued. The Wassermann has always been negative. He returned to work four months after beginning the treatment. He was accidentally injured six months later, with a septic infection, which resulted in death fifty-six hours afterward, though he was reported to have been in good physical condition during this time. Evidently the blood dyscrasia in this case was due to syphilis, though there was no Wassermann reaction at any time the test was made.

ESSENTIAL POINTS IN THE TREATMENT

It may be well to recapitulate some of the essential points that constitute this method of treatment. Rest in bed under as satisfactory circumstances as possible is imperative. A small amount of exercise often retards the progress made and prevents improvement, and this is easily proved in these cases by changing from rest to activity or *vice versa.*

It is invariably necessary to assist digestion artificially, since in pernicious anemia there is no hydrochloric acid in the stomach and it has to be supplied from outside.

Naturally, the conditions present in pernicious anemia do not favor very satisfactory endocrine activity of the glands of internal secretion and products of this kind are particularly in order, especially from the thyroid and adrenal glands. One of the most successful remedies in my hands has been a compound capsule containing hemoglobin and its chief synergists. It is given in increasing doses until the physiological effect is pronounced.

It has been noted that recent cases, as compared with those that have existed during a comparatively longer period, often show more serious losses of hemoglobin than the more chronic cases, but usually they respond more readily to treatment.

Loss of weight during the treatment is usual and varies, depending upon the location of the infection. All the gall bladder cases that have come to my attention have lost more in weight than those in whom mouth and other focal infections were prominent causes. Incidentally, I have noticed that those cases that lost weight under this treatment usually have responded more rapidly in the improvement of the blood picture. The return of the former weight is oftentimes inexplicably delayed.

The administration of the phylacogen not merely serves to stimulate the immunity and antagonize the production of the poisons which are fundamentally responsible for the blood picture, but the peculiar lemon color of the skin disappears following the hypodermic injections of the phylacogen before much improvement is found in the blood picture.

I have had most uniform results from the Mixed Infection Phylacogen. Its use should be continued until no reaction is obtained from the injection. Some cases have had injections for twenty-five days each month for four to nine months before the immunity seemed to be established and the blood picture became normal. An occasional large dose which may be sufficient to cause a slight chill often is of great stimulating benefit after the prolonged use of this remedy. The injections are best made in different parts of the body, and hypodermically.

The prospects in the treatment of pernicious anemia ordinarily are not at all good, and it is clear that persistence is a great factor in the treatment outlined. It is also necessary to supplement the removal of the foci

of infection, and the antagonizing of the results of this infection and increasing the immunity of the body by every other method that seems advisable. This is one reason why endocrine treatment is demanded in all cases. The use of tonics and the continuous application of the principles of good hygiene and elimination naturally should accompany our efforts.

There seems to be no way to disprove the laboratory findings as in each case examinations have been made by more than one laboratory without anyone knowing of the findings of others. Original reports of these different laboratories are all on file and since there is no record of similar treatment for this disease, a bibliography and support from other sources are not within the writer's resources.

XXV

PRACTICAL IDEAS CONCERNING THE ENDOCRINES

By Chas. O. Lowry, M.D., Pasadena, Calif.

The internal secretory glands have become factors of greater significance and clinical importance than ever before, and their study is attracting world-wide attention, especially in an every-day clinical way. The one-time theories concerning them now have been proven to be facts, and in most instances the old-fashioned empirical organotherapy has been supplanted by rational and intelligent procedures.

Endocrinology is the study of the internal secretions of the ductless glands, their influence over bodily functions and systems, and their interdependent relations to each other.

In studying the ductless glands, one is attracted to the thyroid because of its prominence in the literature, and because of its having been so long under the scrutiny of internists, and also because Harrower has given us an easily applied clinical test of its functions, the best and only practical test I have known.

This test depends upon the influence of the thyroid upon the pulse and temperature following standard increasing doses of thyroid administered in a routine manner for several days—a record chart being accurately kept before and after the actual period of gland feeding.

The thyroid has been proven to produce the chief detoxicating hormone of the body, and in cases of cretinism, myxedema and hypothyroidism resulting from some systemic toxemia or due to infection, the administration of thyroid (as substitutive organotherapy) has proven beyond doubt that this supply excites the crippled thyroid to renewed activity, the associated glands to a more normal condition, and the system as a whole to a condition in which it is better able to overcome the toxic influences which have been acting upon it.

In supplying a secretion which is deficient, as in congenital cretinism, or a major hypothyroidism induced by some destroying infection, one is impressed by the modern miracle which is wrought. Two cases of congenital cretinism treated by the author lost their abnormal tendencies, their physical and physiological development progressed to normality, and their mental and moral propensities became very good.

THE PLURIGLANDULAR IDEA

It has been shown that the pluriglandular idea evidently is correct; for when such cases go so far under plain thyroid treatment and apparently reach a standstill, they then improve still further when the proper synergists are utilized. This shows that pluriglandular therapy is best and that there is an interdependency of the different hormones and their actions on the bodily functions and systems. In an experience of about eight years as house physician in an orphan asylum, I verified the value of such treatment on a number of cases.

Aside from the substitutive organotherapy already mentioned, instances of which are now commonplace, we have what is known as the homostimulative method. Hallion's dictum seems to be true, viz.: "when a hormone is given, it supplies a systemic deficiency by increasing the productivity of the gland from which it

was derived; and that it also aids the gland in becoming reëducated and renewed—if anatomicaly and physiologically deficient."

Hustin's experiment is of much interest. He activated a pancreas in a paraffin bath, with secretin; *but only in the presence of blood,* indicating that the hormones themselves are activated in some manner by substances present in the plasma.

The system exerts a selective and an appropriative ability to deliver to its hormone producers the hormones we give to activate and rejuvenate them. We know that oxygen in the lungs enriches the blood; and yet we know that the blood stream is the depot of distribution and that respiration occurs in each cell as it gives to and takes from the blood. As analogous to this well-known physiological process, I firmly believe that we can say that these hormones are vital and elementary; that they are necessary to life because they sustain a balance to the various systems, viz., circulatory, muscular, nervous, digestive, mental and others which are interdependent.

Loeb and Rahtjen have ably demonstrated that in dyshormonism and hypohormonism we find a syndrome of evidence of hypotension or hyposphyxia, muscular and general systemic asthenia, hypodynamia, and that the calcium ions are overbalanced by too many natron ions, thus bringing about a train of nervous symptoms, which may border on and actually develop into insanity. In such cases there is a strong tendency to mental disorders, especially to melancholia, and the main infective cause with which we are so familiar, is *influenza.* The case may be the average simple influenza, or that complicated asthenic group of symptoms consisting of what some one has termed "flumonia," with pharyngitis, neuritis, otitis, nephritis, and, in fact, the disease is called by the French "La

Coquette." This term, indeed, conveys a very vivid and familiar clinical picture.

The terrible depression of this condition is the one outstanding symptom, and, in many cases, it is the pathognomonic feature with which we must deal.

Sajous, Harrower and other authorities have found that hypoadrenia is present in severe infections, and compound organotherapy directed to the necessary support of the depleted glands is the rational treatment for such cases. Especially is this true in the light of my previous statements.

Illustrative of the points in question, I desire to report the following case:

Miss B., a Russian, aged 32 years, had been sick with "flumonia" and had been in the hospital and sent home no less than three times. She did not get proper consideration along the lines which the clinical evidence suggested, for when I saw her she was still suffering from cough, temperature, hyposphyxia, muscular asthenia, nervous exhaustion and a near approach to melancholia. She had to be held up in bed in order to be examined. I found an unresolved lobar pneumonia and the sequelae of influenza which I have enumerated.

Before mentioning the treatment of this case I wish to emphatically state *that accurate diagnosis suggests accurate therapy,* and that the right synergists will make the difference between failure and success in many cases. A microscopical analysis of the sputum in this instance showed the need of the mixed respiratory vaccines. The general asthenia was the index for tonics and reconstructives, such as the triple arsenates with strychnia.

A pleasant environment, good diet, massage and a six weeks' course of supportive pluriglandular therapy reestablished the balancing of the circulatory, muscular and nervous systems, and their allied coworking organs. Under this plan this patient entirely recovered, although when first seen she was very nearly over the line of insanity.

Mr. U., American, grocer, age 36 years, had influenza; was in an automobile wreck in which his nerv-

ous system was shocked by the experience more than the injury, and previously he had been very much overworked. He came to me without an acute symptom. I was unable to detect anything more than a "bankruptcy of nerve force," as Osler has so forcibly called it, and conditions of hyposphyxia. [A condition first described and named by Alfred Martinet of Paris, in which the chief symptom is lack of circulatory tone with poor circulation, low tension, cold extremities and venous stasis.—H. R. H.] The blood pressure was low, both for the systolic and diastolic readings, and bradycardia was present, the pulse being fifty-six. Muscular weakness was apparent, and I wondered whether or not I had a permanent or a temporary myocardial condition to deal with.

Under rest treatment, the tonics and the routine supportive hormone therapy, my patient gained in weight and strength. The heart is now beating seventy-eight to the minute, the muscular and nervous systems are approaching their balance, and my patient will soon go back to work.

One cannot accomplish the desired results in reëducating these hormone-producing glands in a short time, after they have been so seriously affected for so many weeks and by such virulent toxins; and one should not relegate valuable hormone therapy to oblivion without consistent and persistent efforts to obtain their effects for good.

Two of my coworkers have corroborated my findings in numerous experiences, and it would be a useless repetition to go on reporting such cases, especially when there have been so many of them.

ENDOCRINE THERAPY IN SURGERY

Aside from the very practical value of the cases so briefly mentioned, I am going to make a plea for the balancing of these systems before operations are undertaken. One who has been in medical and surgical work for more than half of his life cannot but be impressed with the grave responsibilities of such work.

It is common knowledge that postoperative insanity follows the surgical efforts of the very best men. If these vital hormone producers are working in unison, if the various systems of the organism are in accord, if the calcium and natron ions in the plasma are proportionately correct, then the author claims that such surgical cases will emerge from their operations in greater safety, with more chance for recovery, and with less chance of postoperative mental disturbance.

With this in mind I report another case: Mrs. K., housewife, age 32, had influenza, with all the severe symptoms enumerated in the other cases reported. Under the same organotherapeutic treatment, after three months, she was operated on successfully by the author for anal fissure, hemorrhoids, ventral fixation of the uterus, ovariotomy and appendectomy. The patient had been so very melancholic for so long that it would have been but a step more to mental instability of a pronounced type, while now she is cheerful and is doing her own housework; in fact, is surely and safely approaching a normal condition.

Another case in question followed a street car wreck; cholecystectomy, appendectomy, right pyelitis, separation of many adhesions about Glisson's capsule and the diaphragm—this being followed by pneumonia and diaphragmatic pleurisy. After two years the influenza was acquired, pneumonia again affected the lower lobe of the right lung, and a subdiaphragmatic abscess broke into the bowel and was discharged. The patient then emerged from a long siege of suffering with the sequelae formerly noted.

After a course of pluriglandular therapy, he regained his strength and the systemic balances, and then was able to be operated on for hemorrhoids and anal fissure. To my way of thinking his convalescence was greatly aided by compound organotherapy. Surgeons will find organotherapy a wonderful aid as they learn more about such treatment.

STIMULATING MUSCULAR TONE

McNeile, of Los Angeles, uses the posterior pituitary principle injected directly into the uterus during Caesarean section. This is because it directly stimulates the muscle fibres of the uterus, causing contraction and preventing hemorrhage. He uses it while doing the operation at term, or if done early to relieve, and to sterilize a tuberculous patient (De Lee's operation).

For this effect on muscle fibres it is used also to maintain the heart in myocardial tendencies, to help postoperative shock and to maintain a normal bowel tone and stomach tone to prevent postoperative distention, obstruction, and dilated stomach. The use of pituitrin in properly selected cases will avert many instrumental deliveries from uterine inertia. The injection of adrenalin and normal salt, intravenously (30 m. of 1-1000 solution to one pint), or subcutaneously, is a great help in shock.

As the father of ovariotomy, Dr. Ephraim McDowell became a famous benefactor of womanhood. I honor the toilers who give their all to establish vital facts in surgery and in medicine; these men who triumph despite difficulties and adverse criticism; these intellectural giants who rise high above doubt. There has been no braver act than that of McDowell, who calmly operated while a howling mob, whose attitude was dangerous and malicious, was just outside the humble home. Much unkind and prejudicial propaganda has had to be overcome since that time, and students of organotherapy have had to face much criticism, despite all of which they have courageously gone forward and achieved.

Many have said that these hormones would not be effective if given *per os;* that they would be destroyed by the digestive processes; and that such dosage would be inaccurate. Clinical experience decisively disproves

all of this. The truth is that because these substances possess such important inherent properties, they are not easily destroyed. They are taken up by the lacteals, get to the thoracic duct; are emptied into the subclavian, sent to the lungs, thence to the heart and via the aorta to the parenchymatous cells, or working cells of these glands. The blood stream carries them to where they are utilized. They activate, rejuvenate, restore and benefit the cells, organs and systems and each other as necessary, and as described. When given intravenously, subcutaneously, or intramuscularly, these products must take the same route to be ultimately distributed.

We are sure that these are truths, else thyroid treatment *per os* never would have benefited a suitable patient. This is the best and most thoroughly understood of all reasoning for my position.

Thus organotherapy is a measure which completes McDowell's triumphs. The administration of ovarian substance (corpus luteum, or whole gland), and its synergists (thyroid, if hyperthyroidism is absent, and pituitary) aids as can no other measure thousands of women who have suffered the tortures of an induced menopause.

The fame of the organotherapist goes farther; for in dysovarism, or dyshormonism it may and often does restore and assist normal menstrual function to the degree that operation may be averted.

In the unnatural cases of the menopause, this therapy will aid and has aided many mothers, sisters and wives at the time of life when apprehension, neurasthenia and insanity are most to be feared. Their forces for good will have been conserved for their loved ones, their obligations to their families and to society will have been fulfilled, whereas, without such help thousands of women would have been semi-invalids, or worse.

That these hormones regulate metabolism is now a logical deduction. They regulate and balance the circulation, and no digestive organ can provide nutrition for assimilaton unless its proper blood supply is insured. This being true, when dyshormonism occurs, the other dependent systems (vasomotor, muscular, nervous) suffer, and the tissue wastes remain improperly replenished, secretion and excretion lose their interdependent balance, and the whole body suffers because of it.

If a professional man possesses a well-balanced poise he is the owner of an admirable personality, and the more able to care for responsibilities. How much poise can any man or woman have whose systems are not in accord? Where dyshormonism is dominant, both body and mind must suffer.

As a parting reiteration, I would emphasize the symptoms which clinically portray this lack of systemic poise which governs the body and the mind, viz., hypotension, hypodynamia, and hyponervosa—or hypoasthenia—which is the sum total of all. I would also make a final plea for the already named synergistic supportive treatment, for patience, and for persistence or the necessary time which these potent agencies must have in order to do their work.

My parting declaration is that the early restoration of this deranged hormone balance insures to the patient a greater resistance against tuberculosis, and we know how prone it is to follow pneumonia and influenza.

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XXVI

ANGIONEUROTIC EDEMA: A PLURIGLANDULAR HYPERSECRETORY SYNDROME

By D. M. Green, M.D., Los Angeles, Calif.

Angioneurotic edema, usually classed with the diseases of the nervous system, is, according to Osler's definition,[1] "an affection characterized by the occurrence of local edematous swellings more or less limited in extent, and of transient duration." Quincke[2] regards it as a vasomotor neurosis, under the influence of which the permeability of the vessels is suddenly increased. Hare[3] subscribes to this view in recommending for treatment the use of calcium chloride and magnesium carbonate "to increase blood coagulability" and "to prevent attacks—by an influence on the blood plasma." Schalek[4] classes angioneurotic edema as a form of urticaria, and mentions urticaria hemorrhagica, urticaria tuberosa (giant wheals), and urticaria pigmentosa as unusual forms of the same disease; he also concludes that the lesions are "due to a spasmodic contraction of the blood-vessels under the influence of the vasomotor nerves." Osler[1] recommends the vasodilator nitroglycerine in the treatment. Bandler[5] observes a common definite relationship between menstruation, angioneurotic edema and urticaria, and believes the latter two may be in the nature of anaphylactic phenomena. Several investigators recently have pointed out the close analogy existing between anaphylaxis and hyperthyroidism, and have re-

marked the exhibition by both of vasomotor excitability, dermographism, urticaria and transient edemas. Anaphylaxis is known to be produced by the entrance into the general circulation of protein matter foreign to the human body.[6] It is not definitely known to be due to anything else, yet similar symptoms actually occur in hyperthyroidism.

That excess amounts of thyroid secretion in the general circulation may be one immediate cause of certain urticarias and transient edemas (i. e., anaphylactic-like symptoms) would therefore, on first thought, appear to be plain. Yet it must be recalled that the phenomena under consideration are definitely localized vasoconstrictions; and that the function of vasoconstriction belongs not to the thyroid gland or its secretion, but to the involuntary nervous system and the thyroid antagonists, i. e., the posterior lobe of the hypophysis and the adrenal medullary tissue or chromaffin system. Thyroid secretion per se, if in excess, actually produces vasodilation, and not vasoconstriction. On second thought, therefore, we are convinced that the thyroid cannot alone cause urticarias and transient edemas, but that its antagonists may do so under certain conditions.

It is, therefore, plain that a classification of the various forms of urticaria simply as vasomotor neuroses does not go quite far enough. A disease whose principal symptom is a localized vasoconstriction cannot be regarded solely as a disorder of the nervous system, when at least two different ductless glands are known to produce internal secretions which possess a marked capacity to bring about vasoconstriction. Definite doubts consequently arise as to whether either of the nervous systems plays more than its usual rôle —that of conductor of impulses only—in disorders of this type. Furthermore, it is difficult to conceive how anaphylaxis, recognized as the result of a foreign pro-

teid circulating in the general blood stream—and whose effects, therefore, must be general—can manifest itself in localized wheals and edemas, unless it be that such areas in some manner previously have become peculiarly susceptible to vasoconstricting stimuli, and have needed only the stimulation or irritation afforded by a circulating foreign protein to cause them to develop the urticarial phenomena.

If this be true, what can be the cause of such a peculiarly localized susceptibility? Certainly no disorder of an entire nervous system; nor does it satisfy the mind to say that transitory excesses of the vasoconstricting internal secretions of the adrenal medulla and the posterior lobe of the hypophysis are responsible for these products, like the anaphylaxis—producing foreign proteins, are blood-borne and general in their effect. On the contrary, a particular localized susceptibility toward vasoconstricting stimuli must exist before any circulating general vasoconstricting agent can cause localized, circumscribed areas of vasoconstriction. A definite departure from normal vasomotor control is, therefore, plainly present in every area involved by the urticarial-like eruption.

THE MECHANISM OF VASOMOTOR CONTROL

A review of the mechanism of normal vasomotor control will be of assistance in making clear the possibilities which lie in a departure therefrom. There is ample evidence on hand to warrant the belief that every nonstriated muscle fibre and every organ of the body has a double nerve supply from the involuntary system. Irritation or stimulation of one branch of this system produces relaxation of the nonstriated muscle fibres and dilation of the peripheral blood vessels (peripheral vasodilation), with a resultant decreased blood pressure; stimulation of the other branch causes contraction of the nonstriated muscle fibres,

contraction of blood vessels (peripheral vasoconstriction), and a resultant increased blood pressure.

The simplest and most common examples of general vasomotor nervous control are those of blushing and paling. These phenomena are unquestionably the result of nervous stimulation, via the involuntary system, of the nonstriated muscle fibres existing in the peripheral blood vessels. A mild stimulus, such as a sense of embarrassment, produces a dilation of these vessels, with a resultant flushing of the skin or blushing. A sharper stimulus, such as fright, produces vasoconstriction, or paling instead. The route taken by each type of stimulus of necessity must be via the involuntary nervous system, as the result follows too quickly after the cause for an intermediary to exist.

It is definitely known, also, that the secretion of the thyroid gland is capable of producing vasodilation when taken by mouth, or administered hypodermically, intramuscularly, or intravenously. Its action is via the blood stream and hence must be exerted directly upon the end plates of the dilating fibres of the involuntary system. Hyperthyroid cases exhibit vasodilation as one of their most strongly marked clinical manifestations.

Here, then, are two outstanding causes of general vasodilation: (a) stimulation of vasodilating fibres through the central nervous system direct, and (b) the thyroid secretion via the blood stream. The action of both is exerted on the nerve end-plates of the nonstriated musculature of the blood vessel walls.

Stimulation of the involuntary nervous system causes vasoconstriction as well; but vasoconstriction is a property long since proven to belong also to the internal secretion of the adrenal medulla and of the posterior lobe of the hypophysis or pituitary body. There would appear to exist between the adrenal medulla, the posterior pituitary lobe, and the involuntary nerv-

ous vasoconstricting apparatus—a relationship similar in kind to that existing between the vasodilating apparatus of the involuntary nervous system and the thyroid, but a relationship devoted to a purpose diametrically opposed—namely, reenforced vasoconstriction.

Of the two functions, vasodilation and vasoconstriction, the former is produced most easily. That it succumbs most readily under repeated or severe stimulus unless supported by an adequate rise in thyroid content of the blood, would seem most likely from the natural sequence of events occurring in abnormal as well as normal subjects. Patients with a complete absence of the thyroid show no tendency to blushing or peripheral vasodilation, but on the contrary, are in a state of marked chronic peripheral vasoconstriction. These patients possess an involuntary nervous mechanism inactivated by reason of the absence of the thyroid principle. Mild hypothyroidism shows but little tendency to peripheral vasodilation under nervous stimulation, a constant vasoconstriction of more or less marked degree existing instead; whereas hyperthyroidism shows a constant vasodilation varying in degree with the grade of hyperthyroidism.

[I cannot refrain from remarking here that in hypothyroidism, and especially in the more decided types as *myxedème fruste,* or myxedema, there is always a mechanical factor involved as a result of the mechanical puffing of the cells, the so-called infiltration first emphasized by Hertoghe. To my mind, the local circulatory findings mentioned by the essayist are more mechanical in character than functional or nervous—the cells are dilated and (myx-)edematous and, consequently, the intercellular capillary circulation is almost impossible.—H. R. H.]

The thyroid gland being supplied by nerve filaments from the involuntary system in common with all other

internal organs and glands, is subject to vasodilation under exactly the same conditions as the peripheral circulatory system. Under vasodilative stimulation it increases its discharge of secretion into the blood stream. Vasodilation following stimulation of the involuntary nervous system for a time most certainly is continued and maintained, or at least reenforced, by the stimulating effect of normal amounts of thyroid secretion circulating in the blood; and this effect is most probably exerted upon vasodilator nerve endplates direct. It appears, therefore, that the thyroid is a selective adjuvant to the vasodilator mechanism of the involuntary nervous system, capable of producing the same results as the nervous impulse, more slowly developed, but of greater potentiality for continuous effect. In the production of this result may be included also the secretion of the anterior of the pituitary lobe, a vasodilating agent, but less potent than the thyroid.

The adrenal medulla and the posterior hypophysis function after a similar manner, but with different results. Both extracts of the adrenal medulla and of the posterior lobe of the pituitary body have power to cause contractions of nonstriated muscle fibres, but the pituitary principle appears to have a more pronounced contractile effect upon the musculature of the internal organs, while adrenalin possesses a selective contractile effect upon the muscle fibres of the circulatory system. Approximately three times as much pituitrin as adrenalin, administered intramuscularly or intravenously, is required to produce equivalent results in connection with the control of hemorrhage and the raising of blood pressure. Applied locally, adrenalin is a far more effective hemostatic or local constricting agent than pituitrin. This would indicate with little question the selective action or chromaffin substance secretion upon blood vessels.

All of these particular organs of internal secretion, therefore, seem normally to respond directly to involuntary nerve stimuli and to coöperate with the involuntary nervous system in vasomotor control. Vasodilation occurs under nervous stimulation which bears with it no intimation of danger to the body. Concrete examples are the emotions of embarrassment and anger. Under this type of stimulus the thyroid gland pours out its vasodilating secretion into the blood stream in increased amount, with the result that mild hyperthyroid symptoms supervene for a time. Vasoconstriction, on the contrary, occurs in response to nervous stimulation, which carries with it definite suggestion of danger to the organism. Blood, which might be lost were the peripheral circulation to sustain injury while relaxed or dilated, is hurried from the surfaces into the interior and safer portions of the body. Bodily heat necessary to life is thereby conserved. The classic example of this type of stimulus is fright, either conscious or unconscious. The chromaffin system and the posterior lobe of the pituitary under such an impulse increase their internal secretions and aid in vasoconstriction. The stimulus of vasoconstriction partakes of the nature of a life-conserving measure and will normally supercede any involuntary vasodilating stimulus, which is not concerned in the conservation of life.

A logical scheme of normal vasomotor control, therefore, seems to present itself, i. e., a nervous system for instantaneous reaction, with two separate groups of glands of internal secretion standing ready immediately thereafter to reënforce the reaction required, whether it be vasodilation or vasoconstriction.

This, however, is not all. It is now generally accepted that between the various ductless glands there exists a reciprocal action. The thyroid, the chromaffin tissue, and the posterior lobe of the pituitary all accelerate the processes of metabolism. In this they are in-

terdependent; all act in a somewhat different manner, yet a balance normally exists between them. All are undoubtedly supplied with a double innervation from the involuntary nervous system. Stimulation of one member of the group automatically results in stimulation of the others. The thyroid, being most sensitive, responds most easily to vasodilating stimuli, and readily increases its secretion. Were it checked merely by a cessation of vasodilating stimuli or the registration of a superior vasoconstricting stimulus, it might pour too much secretion into the blood stream and sustain vasodilation to dangerous lengths. An excess of thyroid secretion in the blood stream, however, destroys the normal interglandular balance, and stimulates the antagonistic adrenal medulla and posterior pituitary to increase action. Hyperactivity of these glands in turn automatically inhibits thyroid activity, and their secretions thrown into the blood stream neutralize or inhibit the physiological action of the excess thyroid content therein, tend to overcome vasodilation, and reënforce vasoconstriction.

Such would appear to be the logical mechanism of normal vasomotor control in the healthy individual. Normally there exists a perfect response of the glands of internal secretion to involuntary nervous stimuli, and a perfect balance of activity between such glands themselves. This normal response may be altered and the balance impaired, however, by continuous stimulation, by overexertion, by pronounced physical or mental fatigue, by disease, including focal infection, by severe nervous shock, or by the entrance into the circulatory system of foreign protein matter. Rogers (7) suggests that the end-plates of the involuntary nerves are affected by fatigue, just as are those of the voluntary system. As a voluntary nerve trunk may be irritated by repeated electric shocks until its functionation ceases because of fatigue, so presumably may the more

sensitive involuntary system be subjected to fatigue effects by repeated stimulation, and temporarily be caused to cease functioning. If this be true, the vasomotor control exercised by the involuntary nervous system and the glands of internal secretion may be seriously impaired or even temporarily lost as a result of nerve end-plate fatigue, produced by repeated or intense nervous stimulation or by irritation of whatever sort.

It is easy to conceive that continuation of a stimulus not sufficiently vigorous at once to exhaust or paralyze a nerve end-plate presently will cause it to become irritable. In this condition of irritability this nerve end-plate is then nearer to the limit of its endurance than when quite fresh and untired. If it then be subjected to further stimulation it will become totally fatigued sooner or later. The more powerful the stimulation the quicker the complete fatigue.

Exactly this condition of affairs pertains in every portion of the human body subject to vasodilation and vasoconstriction. Increased wear and tear beyond a certain point, whatever the cause, increases nerve end-plate irritability and lowers its resistance fatigue. That this increased irritability or near-fatigue may be more pronounced in certain parts of the body than in other portions is self-evident. Even different portions of the same structure or same organ, from various causes, may come temporarily to possess different degrees of resistance to fatigue or strain, i. e., may become "tired" to different degrees. In the same structure or organ, therefore, there may exist areas whose vasodilators, not suffering from irritability, respond normally to a given impulse, and which exhibit little flushing and no swelling; and other areas whose vasodilators have become supersensitive or irritable, which respond excessively, become reddened and flushed to a marked degree and show evidences of beginning swelling or edematous in-

filtration. Similarly, if stimulation of this structure be continued in the same manner, the areas of normal response presently will become irritable, flush markedly and perhaps show beginning edema, while areas previously irritable will become temporarily incapable of responding to vasodilator stimuli.

As has been shown, vasoconstriction is an automatic protective function, capable of operating under conditions which temporarily disrupt peripheral vasodilation. Areas whose vasodilator nerve end-plates from any cause have become temporarily paralyzed or completely fatigued are immediately subject to automatic vasoconstriction. Vasoconstrictors unopposed cause a sharp vasoconstriction in exactly the same manner that the muscles on the sound side of a face affected by facial paralysis automatically contract and pull the mouth toward the sound side, because of the loss of balancing tonicity in the muscles of the paralyzed side. This automatic localized vasoconstriction will continue until the local vasoconstrictors in turn become fatigued or vasodilating tonus returns. Thus a given urticaria-like wheal may be assumed to develop because of localized vasodilation with prompt fatigue-paralysis of the irritated vasodilating end-plates thereafter; and to be caused to persist through antagonistic vasoconstriction of the same vessels, which condition prevents the prompt reabsorption of serum locally exuded through overpermeable vessel walls during dilation.

Not always is such a relatively slow process required to cause localized vasoconstriction. A powerful vasoconstricting nervous impulse, such as fright, or the entrance into the general circulation of a potent foreign protein, may suddenly overwhelm the vasodilating apparatus and produce a sudden generalized vasoconstriction, as in anapyhylactic shock, in which wheals do not occur. Under such circumstances recovery is made by all parts of the body with more or less facility except

those areas whose vasodilators previously have been irritable and near fatigue, or whose vasoconstrictors have been irritable and respond to stimuli in an exaggerated manner before giving way to fatigue. Under such circumstances the formation of a wheal could not occur, as no increased permeability of the vessel walls has occurred. Where localized vasodilation has preceded fatigue, wheal formation may be expected, due to localized vessel-wall permeability. Once established, whether preceding or following wheal formation, local areas of vasoconstriction persist, if undisturbed by treatment, until the local vasoconstrictors in turn become fatigued, when relaxation supervenes and the lesion disappears. That the disappearance of the local vasoconstriction and wheal is due to fatigue paralysis of the local vasoconstricting nerve end-plates would seem to be proven by the fact that local anesthesia produced by sponging the affected surface lightly with chloroform will cause much more rapid disappearance of wheals.

The part played by the posterior lobe of the pituitary body in this series of phenomena does not become apparent in the milder varieties of urticaria, but in the severer forms is often plainly evident in the severe diarrhea, colic, and other gastrointestinal manifestations related to unusual peristaltic action or an excessive contractility of the non-striated musculature.

Vasoconstrictor fatigue necessarily would be swift and the disappearance of wheals prompt, were the affected vasoconstrictors not supported and sustained in their contraction by some agency external to themselves. As previously pointed out, that agency in the body which possesses this ability to the most marked degree, i. e., selective contractile effect upon the muscle fibres of the circulatory system, is adrenin, the product of the adrenal medulla. It would appear, therefore, that long-persisting urticarial wheals, like those of

angioneurotic edema, could not possibly continue as they do without the action of some such adjuvant; and that the source of this adjuvant is the adrenal glands seems most logical. Whether its effect is exerted through the blood stream, in the form of adrenin, as we know it, or is brought about through some as yet not fully-understood action of the gland upon the nervous system, cannot be said with any degree of certainty; yet, whatever be the means of transmission, the preponderance of circumstantial evidence points to the adrenal medulla as the source of the impulse which causes the persistence of long-lived urticaria-like lesions. *In other words, hyperadrenia most probably is the cause of the persistence of angioneurotic edematous lesions.*

What then is the cause of the lesions themselves? As has been pointed out, we know that ordinary urticaria is preceded by the introduction into the system and the blood stream of foreign protein of whatever kind, and that angioneurotic edema usually is preceded by fright or other nervous shock, by sudden imposition of responsibility or other worry, or by exertion to the point of fatigue. In the first case probably only the foreign protein is a factor. Yet, since urticarias do not develop except where elimination is suddenly decreased, the normal alkali reserve of the body lowered, and acidosis of degree exists, the addition of a foreign protein represents an increased wear and tear upon all parts of the system, and thus places added demands upon the detoxicating apparatus of which the thyroid gland is a prominent factor. To terminal vessel walls already irritated by increased blood-borne wastes comes added irritation in the form of a new foreign protein. To them likewise come added vasodilating impulses from increased thyroid functioning. Here and there in terminal vessel walls fatigue of vasodilators supervenes, often precipitated by external irritation, such as

scratching and rubbing, and with this fatigue the permeability of the wall increases with resultant limited serum oozing, i. e., wheal formation.

In simple urticarias this wheal formation is of short duration. With no marked vasoconstricting impulse ensuing, tonus gradually returns to the fatigued vasodilators, increased vessel wall permeability disappears, exuded serum is taken up by the normal processes of tissue drainage, and the wheal fades. It is unlikely that local deposits of toxins and osmosis thereto enter into the creation of such lesions, since disappearance of the wheal follows so promptly upon the cessation of external irritation.

Here then it would seem that hyperthyroid action plus local vasodilator fatigue are the direct cause of simple urticarial lesions.

Between the short-lived manifestations of simple urticaria and the long-lived lesions of angioneurotic edema there appear to be differences only as to the exciting cause and the duration of the individual swellings. In the angioneurotic type nervous stress or fatigue seem to be the predominating features in the etiology. We know these factors, absent in simple urticatria, cause profound adrenal irritation, rather than thyroid stimulation. Adrenal excitation, however, always entails thyroid stimulation, so that in angioneurotic types thyroid stimulation is present. Furthermore, in profound nervous excitation or fatigue, digestion often is curtailed or temporarily stopped, and proteins, whose digestion is interfered with, may be assimilated later in forms particularly irritating to the organism, and capable of producing as components of the blood any or all the phenomena ascribed to foreign proteins in the blood, including both thyroid and adrenal irritation. Except in cases of severe nervous reaction a temporary hyperthyroid secretion either occurs first or quickly supervenes after

acute adrenal irritation; and the adrenal irritation in angioneurotic edema appears never to be of a type severe enough to overcome local vasodilation until the local vasodilators are paralyzed through fatigue. Yet, once local vasodilator paralysis has occurred, adrenal support of the unopposed vasoconstriction results in a severe and long-continued angiospasm and interruption of the circulation in the involved area, the end product of which is a large, persistent wheal—*the true lesion of angioneurotic edema.* All evidence, therefore, points to a primarily predominating vasodilator irritability (hyperthyroid phenomenon) to which has been added a powerful continuing constricting impulse (hyperadrenal phenomenon) as being the direct causes of angioneurotic edema.

These facts and circumstances show conclusively the endocrine factor in angioneurotic edema, and appear to the author to reveal thyro-adrenal irritation as the real cause thereof. Neuromuscular fatigue of the vessel walls appears to be merely an incidental circumstance which makes possible localized vessel-wall permeability and the resultant serum oozing. The cause of augmented vasodilation and reënforced vasoconstriction logically must be the real cause of this disorder, which might better be known as "Thyro-Adrenal Urticaria," a pluriglandular hypersecretory syndrome.

An added evidence of the predominance of adrenal hypersecretion in this condition lies in the uniform existence in angioneurotic edema of a lowered sugar tolerance and a glycosuria of small degree. Animal experimentation has shown (8) that extreme glycosuria may be produced by adrenin injections.

Treatment: The treatment should be that of mild hyperthyroidism and lowered sugar tolerance, plus free elimination, alkalies to restore the normal alkali reserve, a large fluid intake, local sedation, and physical and mental rest. Many patients are particularly sen-

sitive to foreign proteins of any kind, either in the form of food or medicines, and these patients may require desensitization by the Besredka (9) method or modification before biological products can be used. The carbohydrate intake should be carefully regulated in accordance with urinary findings. Of the endocrine products, parathyroid gland to control neuromuscular unbalance, and pancreas substance to reëstablish normal work of the pancreas and antagonize the adrenals are directly indicated.

Thyroidectomized horse serum, while indicated as a thyroid antagonist, almost invariably serves as a direct exciting cause of increased attacks of angioneurotic edema by reason of the protein-bearing serum. Thyroidectin in 5-grain capsules, three times daily, is better borne. The following prescriptions have been used with success by the writer:

℞: Quinine Hydrobromide .....gr. v
Iron Arsenate .....gr. 1/10
Atropine Sulphate .....gr. 1/1000
M. et ft. tales Caps. No. 100.
Sig: One capsule three times daily, at meals.

℞: Parathyroid Gland, Desiccated.....gr. ss
Pancreas, Desiccated .....gr. ij
Bile Salts, Powdered.....gr. j
Calcium Lactate .....gr. jss
M. et ft. tales Caps. No. 100.
Sig: Two capsules four times a day between meals.

RÉSUMÉ

Angioneurotic edema is a pluriglandular hypersecretory syndrome, in which thyroid excess is a preliminary feature and adrenal hyperactivity the secondary and predominating characteristic.

Local wheal formation develops because of localized vasodilation of thyroid origin, with prompt subsequent fatigue-paralysis of the irritated vasodilating nerve end-plates and increased vessel-wall permeability, whereby blood-serum oozes into the surrounding tissues; it persists through primary antagonistic vaso-

constriction of the same vessels, with secondary support and prolongation by adrenal hyperactivity, which vasoconstriction limits the blood supply to the affected part and for a continued period prevents the reabsorption of exuded serum.

Foreign protein in the blood stream appears to be the exciting cause of thyroid activity and vasodilator irritability and near-fatigue; nervous shock, continued strain and fatigue appear to be the exciting causes of adrenal hyperactivity. The latter are absent in simple urticaria, hence adrenal hyperactivity is absent and wheal persistence is slight; in angioneurotic edema any or all are present, hence adrenal hyperactivity is present, and wheal persistence is great. In both types of urticaria foreign protein absorption manifestations are marked.

Being of thyroid and adrenal origin, and not a disease of the nervous system, angioneurotic edema should be known as Thyro-Adrenal Urticaria.

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